HEPATOCYTE NUCLEAR FACTOR 4α MODULATOR COMPOUNDS

RELATED APPLICATIONS

[001] This application claims the benefit of priority of U.S. Provisional Application Ser. No. 60/488,237 filed July 16, 2003, the entire disclosure of which is incorporated herein by reference.

TECHNICAL FIELD

[002] This invention relates to compounds that bind to and/or modulate hepatocyte nuclear factor 4α receptors and to methods for making and using such compounds.

BACKGROUND

[003] Hepatocyte nuclear factor 4α (HNF-4α) has been described as a member of the steroid/thyroid superfamily of transcription factors that is expressed in liver, kidney, intestine and pancreas. Sladek*et al.*, (1990) *Genes Dev.* **4**, 2353-2365; Miquerol *et al.*, (1994) *J. Biol. Chem.* **269**:8944-8951. No ligand has been identified at present and therefore HNF-4α is referred to as an orphan member of the intracellular receptor family (3-5). Tsai & O'Malley (1994) *Annu. Rev. Biochem.* **63**: 451-486; Mangelsdorf & Evans (1995) *Cell* **83**:841-850; Kastner *et al* (1995) *Cell* **83**:859-869.

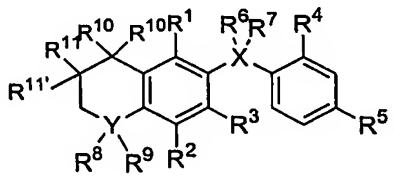
[004] HNF-4α has been described as being capable of activating transcription in tissue culture cells under certain conditions. Kou *et al.*, (1992) *Nature* **355**:457-461; Ladias *et al.*, (1992) *J. Biol. Chem.* 267:15849-15860; Mietus-Snyder *et al.*, (1992) *Mol. Cell. Biol.* 12:1708-1718; Metzger *et al.*,. (1993) *J. Biol. Chem.* **268**:16831-16838. It has been suggested that HNF-4α plays a role in one or more metabolic pathways,

including glucose and lipid homeostasis. Ladias *et al.*, (1992) *J. Biol. Chem.* **267**:15849-15860; Mietus-Snyder *et al.*, (1992) *Mol. Cell. Biol.* **12**:1708-1718; Metzger *et al.*, (1993) *J. Biol. Chem.* **268**:16831-16838; Yamagata *et al.*, (1996) *Nature* **384**, 458-460; Stoffel & Duncan (1997) *Proc. Natl. Acad. Sci. U.S.A.* **94**, 13209-13214.

[005] Certain mutations of HNF-4α result in defective function of the endocrine pancreas and maturity-onset diabetes of the young (MODY1), suggesting that HNF-4 α plays a role in metabolic gene regulation. Yamagata *et al.*, (1996) *Nature* **384**;458-460. Liver-specific knockouts demonstrate that HNF-4α plays a role in liver development and function. Li *et al.*, (2000) *Genes & Dev.* **14**:464-474; Hayhurst *et al.*, (2001) *Mol. Cell. Biol.* **21**:1393-1403; Fraser (1998) *Nuc. Acids Res.* **26**:2702-2707.

SUMMARY OF THE INVENTION

[006] In certain embodiments, the present invention provides a compound of formula I:



or a pharmaceutically acceptable salt, ester, amide, or prodrug thereof,

wherein:

R^1 is selected from H, a halogen, SH, and OH;

R^2 is selected from H, a halogen, a $NR^{12}R^{13}$, a sulfonamide, a nitro, a formyl, an acyl, a C_1-C_3 alkyl optionally substituted with one or more fluorines, a C_2-C_3 alkenyl optionally substituted with one or more fluorines, a C_2-C_3 akynyl optionally substituted with one or more fluorines, a C_1-C_2 alkoxy optionally substituted with one or more fluorines, a C_1-C_2 thioalkyl optionally substituted with one or more fluorines, a C_2 thioalkenyl optionally substituted with one or more fluorines, a C_2 thioakynyl optionally substituted with one or more fluorines, and a hydroxylamine optionally substituted with a C_1-C_2 alkyl, a C_2 alkenyl, C_2 akynyl, a C_1-C_2 fluoroalkyl, a C_2 fluoroalkenyl, or a C_2 fluoroakynyl;

R^3 is selected from H, a halogen, a nitro, a C_1-C_{10} alkyl optionally substituted with one or more halogens, a C_2-C_{10} alkenyl optionally substituted with one or more halogens, a C_2-C_{10} akynyl optionally substituted with one or more halogens, a C_1-C_{10} alkoxy optionally substituted with one or more halogens, a C_1-C_{10} thioalkyl optionally substituted with one or more halogens, a C_2-C_{10} thioalkenyl optionally substituted with one or more halogens, a C_2-C_{10} thioakynyl optionally substituted with one or more fluorines, a $NR^{14}R^{15}$, and a five to six-membered carbocyclic or heterocyclic ring optionally substituted with up to two R^{19} groups;

R^4 is selected from H, a halogen, and OH;

R^5 is selected from CH_2OH, CHO, COOH, and a $C(R^{5'})(R^{5''})(COOH)$;

$R^{5'}$ and $R^{5''}$ are each independently selected from H, O, S and F; or $R^{5'}$ and $R^{5''}$ together form an O or S;

R^6 and R^7 are each independently selected from H, a halogen, a C_1-C_{12} alkyl optionally substituted with one or more R^{19}, a C_2-C_{12} alkenyl optionally substituted with one or more R^{19}, a C_2-C_{12} akynyl optionally substituted with one or more R^{19}, a C_1-C_{12} alkoxy optionally substituted with one or more R^{19}, a C_1-C_{12} thioalkyl optionally substituted with one or more R^{19}, a C_2-C_{12} thioalkenyl optionally substituted with one or more R^{19}, a C_2-C_{12} thioakynyl optionally substituted with one or more R^{19}, a $NR^{16}R^{17}$, a $NHC(O)R^{18}$ and null; or R^6 and R^7 taken together form an O, S, NH or CH_2;

R^8 and R^9 are each independently selected from H, a halogen, a methyl optionally substituted with one or more halogens, and null; or R^8 and R^9 taken together with Y form a three to five-membered optionally substituted carbocyclic ring;

each R^{10} is independently selected from H, a halogen, and a methyl optionally substituted with one or more halogens;

R^{11} and $R^{11'}$ are each independently selected from H, a halogen and OH; or R^{11} and $R^{11'}$ taken together form an O;

R^{12} and R^{13} are each independently a C_1-C_3 alkyl optionally substituted with one or more halogens, a C_2-C_3 alkenyl optionally substituted with one or more halogens, or a C_2-C_3 akynyl optionally substituted with one or more halogens; or R^{12} and R^{13} taken together with the nitrogen atom to which they are both bound form a five to six-membered heterocyclic ring;

R^{14} and R^{15} are each independently a C_1-C_2 alkyl optionally substituted with one or more halogens, a C_2 alkenyl optionally substituted with one or more halogens, or a C_2 akynyl optionally substituted with one or more halogens;

R^{16} and R^{17} are each independently selected from a C_1-C_{12} alkyl optionally substituted with one or more R^{19}, a C_2-C_{12} alkenyl optionally substituted with one or more R^{19}, a C_2-C_{12} akynyl optionally substituted with one or more R^{19}, and a five to six-membered carbocyclic or heterocyclic ring optionally substituted with one or more R^{19}; or R^{16} and R^{17} taken together with the nitrogen atom to which they are both bound form a five to six-membered heterocyclic ring;

R^{18} is selected from a C_1-C_{10} alkyl optionally substituted with one or more halogens, a C_2-C_{10} alkenyl optionally substituted with one or more halogens, a C_2-C_{10} akynyl optionally substituted with one or more halogens, and a five to six-membered carbocyclic or heterocyclic ring optionally substituted with one or more R^{19};

R^{19} is selected from a halogen, a C_1-C_4 alkyl optionally substituted with one or more fluorines, a C_2-C_4 alkenyl optionally substituted with one or more fluorines, a C_2-C_4 akynyl optionally substituted with one or more fluorines, a C_1-C_4 alkoxy optionally substituted with one or more halogens, a C_1-C_3 thioalkyl optionally substituted with one or more halogens, a C_2-C_3 thioalkenyl optionally substituted with one or more halogens, C_2-C_3 thioakynyl optionally substituted with one or more halogens, a formyl and a nitro;

X and Y are each independently selected from O, S, N and C;

wherein:

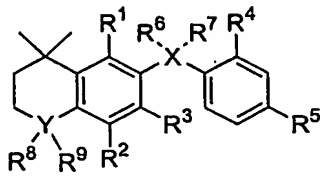
if X is O or S, then each of R^6 and R^7 is null;

if X is N, then one of R^6 and R^7 is null;

if Y is O or S, then each of R^8 and R^9 is null; and

if Y is N, then one of R^8 and R^9 is null.

[007] In certain embodiments, the invention provides a compound of formula II:



II

or a pharmaceutically acceptable salt, ester, amide, or prodrug thereof,

wherein:

R^1 is selected from H, a halogen, SH, and OH;

R^2 is selected from H, a halogen, a $NR^{12}R^{13}$, a sulfonamide, a nitro, a formyl, an acyl optionally substituted with one or more halogens, a C_1-C_3 alkyl optionally substituted with one or more fluorines, a C_2-C_3 alkenyl optionally substituted with one or more fluorines, a C_2-C_3 akynyl optionally substituted with one or more fluorines, a C_1-C_2 alkoxy optionally substituted with one or more fluorines, a C_1-C_2 thioalkyl optionally substituted with one or more fluorines, a C_2 thioalkenyl optionally substituted with one or more fluorines, a C_2 thioakynyl optionally substituted with one or more fluorines, and a hydroxylamine optionally substituted with a C_1-C_2 alkyl, a C_2 alkenyl, a C_2 akynyl, a C_1-C_2 fluoroalkyl, a C_2 fluoroalkenyl, or C_2 fluoroakynyl;

R^3 is selected from H, a halogen, a nitro, a C_1-C_{10} alkyl optionally substituted with one or more halogens, a C_2-C_{10} alkenyl optionally substituted with one or more halogens, a C_2-C_{10} akynyl optionally substituted with one or more halogens, a C_1-C_{10} alkoxy optionally substituted with one or more halogens, a C_1-C_{10} thioalkyl optionally

substituted with one or more halogens, a C_2-C_{10} thioalkenyl optionally substituted with one or more halogens, a C_2-C_{10} thioakynyl optionally substituted with one or more halogens, a $NR^{14}R^{15}$, and a five to six-membered carbocyclic or heterocyclic ring optionally substituted with up to two R^{19} groups;

R^4 is selected from H, a halogen, and OH;

R^5 is selected from CH_2OH, CHO, COOH, and a $C(R^{5'})(R^{5''})(COOH)$;

$R^{5'}$ and $R^{5''}$ are each independently selected from H, O, S and F; or $R^{5'}$ and $R^{5''}$ together form an O or S;

R^6 and R^7 are each independently selected from H, a halogen, a C_1-C_{12} alkyl optionally substituted with one or more R^{19}, a C_2-C_{12} alkenyl optionally substituted with one or more R^{19}, a C_2-C_{12} akynyl optionally substituted with one or more R^{19}, a C_1-C_{12} alkoxy optionally substituted with one or more R^{19}, a C_1-C_{12} thioalkyl optionally substituted with one or more R^{19}, a C_2-C_{12} thioalkenyl optionally substituted with one or more R^{19}, a C_2-C_{12} thioakynyl optionally substituted with one or more R^{19}, a $NR^{16}R^{17}$, a $NHC(O)R^{18}$ and null; or R_6 and R_7 taken together form an O, S, NH or CH_2;

R^8 and R^9 are each independently selected from H, halogen, a methyl optionally substituted with one or more halogens, and null; or R^8 and R^9 taken together with Y form a three to five-membered optionally substituted carbocyclic ring;

R^{12} and R^{13} are each independently a C_1-C_3 alkyl optionally substituted with one or more halogens, a C_2-C_3 alkenyl optionally substituted with one or more halogens, or a C_2-C_3 akynyl optionally substituted with one or more halogens; or R^{12} and R^{13} taken

together with the nitrogen atom to which they are both bound form a five to six-membered heterocyclic ring;

R^{14} and R^{15} are each independently a C_1-C_2 alkyl optionally substituted with one or more halogens, a C_2 alkenyl optionally substituted with one or more halogens, or a C_2 akynyl optionally substituted with one or more halogens;

R^{16} and R^{17} are each independently selected from a C_1-C_{12} alkyl optionally substituted with one or more R^{19}, a C_2-C_{12} alkenyl optionally substituted with one or more R^{19}, a C_2-C_{12} akynyl optionally substituted with one or more R^{19}, and a five to six-membered carbocyclic or heterocyclic ring optionally substituted with one or more R^{19}; or R^{16} and R^{17} taken together with the nitrogen atom to which they are both bound form a five to six-membered heterocyclic ring;

R^{18} is selected from a C_1-C_{10} alkyl optionally substituted with one or more halogens, a C_2-C_{10} alkenyl optionally substituted with one or more halogens, a C_2-C_{10} akynyl optionally substituted with one or more halogens, and a five to six-membered carbocyclic or heterocyclic ring optionally substituted with one or more R^{19};

R^{19} is selected from a halogen, a C_1-C_4 optionally substituted with one or more fluorines, a C_2-C_4 alkenyl optionally substituted with one or more fluorines, a C_2-C_4 akynyl optionally substituted with one or more fluorines, a C_1-C_4 alkoxy optionally substituted with one or more halogens, a C_1-C_3 thioalkyl optionally substituted with one or more halogens, a C_2-C_3 thioalkenyl optionally substituted with one or more halogens, a C_2-C_3 thioakynyl optionally substituted with one or more halogens, a formyl and a nitro;

X and Y are each independently selected from O, S, N and C;

wherein:

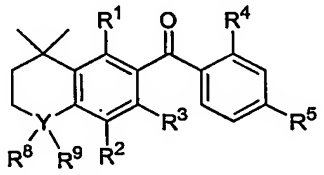
if X is O or S, then each of R^6 and R^7 is null;

if X is N, then one of R^6 and R^7 is null;

if Y is O or S, then each of R^8 and R^9 is null; and

if Y is N, then one of R^8 and R^9 is null.

[008] In certain embodiments, the invention provides a compound of formula III:



III

or a pharmaceutically acceptable salt, ester, amide, or prodrug thereof,

wherein

R^1 is selected from H, a halogen, SH, and OH;

R^2 is selected from H, a halogen,a $NR^{12}R^{13}$, a sulfonamide, a nitro, a formyl, an acyl optionally substituted with one or more halogens, a C_1-C_3 alkyl optionally substituted with one or more fluorines, a C_2-C_3 alkenyl optionally substituted with one or more fluorines, a C_2-C_3 akynyl optionally substituted with one or more fluorines, a C_1-C_2 alkoxy optionally substituted with one or more fluorines, a C_1-C_2 thioalkyl optionally

substituted with one or more fluorines, a thioC_2 alkenyl optionally substituted with one or more fluorines, a C_2 thioakynyl optionally substituted with one or more fluorines, and a hydroxylamine optionally substituted with a C_1-C_2 alkyl, a C_1- C_2 alkenyl, a C_2 akynyl, a C_1-C_2 fluoroalkyl, a C_2 fluoroalkenyl, or a C_2 fluoroakynyl;

R^3 is selected from H, a halogen, a nitro, a C_1-C_{10} alkyl optionally substituted with one or more halogens, a C_2-C_{10} alkenyl optionally substituted with one or more halogens, a C_2-C_{10} akynyl optionally substituted with one or more halogens, a C_1-C_{10} alkoxy optionally substituted with one or more halogens, a C_1-C_{10} thioalkyl optionally substituted with one or more halogens, a C_2-C_{10} thioalkenyl optionally substituted with one or more halogens, C_2-C_{10} thioakynyl optionally substituted with one or more halogens, a $NR^{14}R^{15}$, and a five to six-membered carbocyclic or heterocyclic ring optionally substituted with up to two R^{19} groups;

R^4 is selected from H, a halogen, and OH;

R^5 is selected from CH_2OH, CHO, COOH, and a $C(R^{5'})(R^{5''})(COOH)$;

$R^{5'}$ and $R^{5''}$ are each independently selected from H, O, S and F; or $R^{5'}$ and $R^{5''}$ together form an O or S;

R^8 and R^9 are each independently selected from H, a halogen, a methyl optionally substituted with one or more halogens, and null; or R^8 and R^9 taken together with Y form a three to five-membered optionally substituted carbocyclic ring;

R^{12} and R^{13} are each independently a C_1-C_3 alkyl optionally substituted with one or more halogens, a C_2-C_3 alkenyl optionally substituted with one or more halogens, or a

C_2-C_6 akynyl optionally substituted with one or more halogens; or R^{12} and R^{13} taken together with the nitrogen atom to which they are both bound form a five to six-membered heterocyclic ring;

R^{14} and R^{15} are each independently a C_1-C_2 alkyl optionally substituted with one or more halogens, a C_2 alkenyl optionally substituted with one or more halogens, or a C_2 akynyl optionally substituted with one or more halogens;

R^{19} is selected from a halogen, a C_1-C_4 alkyl optionally substituted with one or more fluorines, a C_2-C_4 alkenyl optionally substituted with one or more fluorines, a C_2-C_4 akynyl optionally substituted with one or more fluorines, a C_1-C_4 alkoxy optionally substituted with one or more halogens, a C_1-C_3 thioalkyl optionally substituted with one or more halogens, a C_2-C_3 thioalkenyl optionally substituted with one or more halogens, a C_2-C_3 thioakynyl optionally substituted with one or more halogens, a formyl and a nitro;

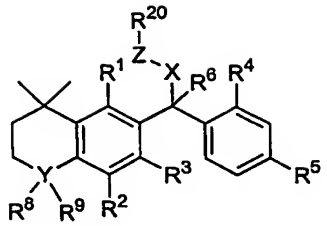
Y is selected from O, S, N and C;

wherein:

if Y is O or S, then each of R^8 and R^9 is null; and

if Y is N, then one of R^8 and R^9 is null.

[009] In certain embodiments, the invention provides a compound of formula IV:



IV

or a pharmaceutically acceptable salt, ester, amide, or prodrug thereof,

wherein:

R^1 is selected from H, a halogen, SH, and OH;

R^2 is selected from H, a halogen, a $NR^{12}R^{13}$, a sulfonamide, a nitro, a formyl, an acyl, a C_1-C_3 alkyl optionally substituted with one or more fluorines, a C_2-C_3 alkenyl optionally substituted with one or more fluorines, a C_2-C_3 akynyl optionally substituted with one or more fluorines, a C_1-C_2 alkoxy optionally substituted with one or more fluorines, a C_1-C_2 thioalkyl optionally substituted with one or more fluorines, a C_2 thioalkenyl optionally substituted with one or more fluorines, a C_2 thioakynyl optionally substituted with one or more fluorines, and a hydroxylamine optionally substituted with a C_1-C_2 alkyl, a C_2 alkenyl, a C_2 akynyl, a C_1-C_2 fluoroalkyl, a C_2 fluoroalkenyl, or a C_2-C_6 fluoroakynyl;

R^3 is selected from H, a halogen, a nitro, a C_1-C_{10} alkyl optionally substituted with one or more halogens, a C_2-C_{10} alkenyl optionally substituted with one or more halogens, a C_2-C_{10} akynyl optionally substituted with one or more halogens, a C_1-C_{10} alkoxy optionally substituted with one or more halogens, a C_1-C_{10} thioalkyl optionally substituted with one or more halogens, a C_2-C_{10} thioalkenyl optionally substituted with one or more halogens, C_2-C_{10} thioakynyl optionally substituted with one or more

halogens, a $NR^{14}R^{15}$, and a five to six-membered carbocyclic or heterocyclic ring optionally substituted with up to two R^{19} groups;

R^4 is selected from H, a halogen, and OH;

R^5 is selected from CH_2OH, CHO, COOH, and a $C(R^{5'})(R^{5''})(COOH)$;

$R^{5'}$ and $R^{5''}$ are each independently selected from H, O, S or F; and $R^{5'}$ and $R^{5''}$ together form an O or S;

R^6 is selected from H, a halogen, a C_1-C_{12} alkyl optionally substituted with one or more R^{19}, a C_2-C_{12} alkenyl optionally substituted with one or more R^{19}, a C_2-C_{12} akynyl optionally substituted with one or more R^{19}, a C_1-C_{12} alkoxy optionally substituted with one or more R^{19}, a C_1-C_{12} thioalkyl optionally substituted with one or more R^{19}, a C_2-C_{12} thioalkenyl optionally substituted with one or more R^{19}, a C_2-C_{12} thioakynyl optionally substituted with one or more R^{19},a $NR^{16}R^{17}$, a $NHC(O)R^{18}$ and null;

R^8 and R^9 are each independently selected from H, a halogen, a methyl optionally substituted with one or more halogens, and null; or R^8 and R^9 taken together with Y form a three to five-membered optionally substituted carbocyclic ring;

R^{12} and R^{13} are each independently a C_1-C_3 alkyl optionally substituted with one or more halogens, a C_2-C_3 alkenyl optionally substituted with one or more halogens, or C_2-C_3 akynyl optionally substituted with one or more halogens; or R^{12} and R^{13} taken together with the nitrogen atom to which they are both bound form a five to six-membered heterocyclic ring;

R^{14} and R^{15} are each independently a C_1-C_2 alkyl optionally substituted with one or more halogens, a C_2 alkenyl optionally substituted with one or more halogens, or a C_2 akynyl optionally substituted with one or more halogens;

R^{16} and R^{17} are each independently selected from a C_1-C_{12} alkyl optionally substituted with one or more R^{19}, a C_2-C_{12} alkenyl optionally substituted with one or more R^{19}, a C_2-C_{12} akynyl optionally substituted with one or more R^{19}, and a five to six-membered carbocyclic or heterocyclic ring optionally substituted with one or more R^{19}; or R^{16} and R^{17} taken together with the nitrogen atom to which they are both bound form a five to six-membered heterocyclic ring;

R^{18} is selected from a C_1-C_{10} alkyl optionally substituted with one or more halogens, a C_2-C_{10} alkenyl optionally substituted with one or more halogens, a C_2-C_{10} akynyl optionally substituted with one or more halogens, and a five to six-membered carbocyclic or heterocyclic ring optionally substituted with one or more R^{19};

R^{19} is selected from a halogen, a C_1-C_4 alkyl optionally substituted with one or more fluorines, a C_2-C_4 alkeny optionally substituted with one or more fluorines l, a C_2-C_4 akynyl optionally substituted with one or more fluorines, a C_1-C_4 alkoxy optionally substituted with one or more halogens, a C_1-C_3 thioalkyl optionally substituted with one or more halogens, a C_2-C_3 thioalkenyl optionally substituted with one or more halogens, a C_2-C_3 thioakynyl optionally substituted with one or more halogens, a formyl and a nitro;

R^{20} is selected from a C_4-C_5 alkyl optionally substituted with one or more halogens, a C_4-C_5 alkenyl optionally substituted with one or more halogens, a C_4-C_5

akynyl optionally substituted with one or more halogens, a phenyl optionally substituted with one or more fluorines, a thienyl optionally substituted with one or more fluorines, and a benzyl optionally substituted with one or more R^{19};

X is selected from O and NH;

Y is selected from O, S, N, and C; and

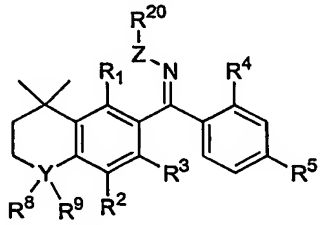
Z is selected from CH_2, NH, and phenylene;

wherein:

if Y is O or S, then each of R^8 and R^9 is null; and

if Y is N, then one of R^8 and R^9 is null.

[010] In certain embodiments, the invention provides a compound of formula V:



V

or a pharmaceutically acceptable salt, ester, amide, or prodrug thereof,

wherein:

R^1 is selected from H, a halogen, SH, and OH;

R^2 is selected from H, a halogen, a $NR^{12}R^{13}$, a sulfonamide, a nitro, a formyl, an acyl, a C_1-C_3 alkyl optionally substituted with one or more fluorines, a C_2-C_3 alkenyl

optionally substituted with one or more fluorines, a C_2-C_3 akynyl optionally substituted with one or more fluorines , a C_1-C_2 alkoxy optionally substituted with one or more fluorines, a C_1-C_2 thioalkyl optionally substituted with one or more fluorines, a C_2 thioalkenyl optionally substituted with one or more fluorines, a C_2- thioakynyl optionally substituted with one or more fluorines, and a hydroxylamine optionally substituted with a C_1-C_2 alkyl, a C_2 alkenyl, a C_2 akynyl, a C_1-C_2 fluoroalkyl, a C_2 fluoroalkenyl, or a C_2 fluoroakynyl;

R^3 is selected from H, a halogen, a nitro, a C_1-C_{10} alkyl optionally substituted with one or more halogens C_2-C_{10} alkenyl optionally substituted with one or more halogens, C_2-C_{10} akynyl optionally substituted with one or more halogens, a C_1-C_{10} alkoxy optionally substituted with one or more halogens, a C_1-C_{10} thioalkyl optionally substituted with one or more halogens, a C_2-C_{10} thioalkenyl optionally substituted with one or more halogens, a C_2-C_{10} thioakynyl optionally substituted with one or more halogens, a $NR^{14}R^{15}$, and a five to six-membered carbocyclic or heterocyclic ring optionally substituted with up to two R^{19} groups;

R^4 is selected from H, a halogen, and OH;

R^5 is selected from CH_2OH, CHO, COOH, and a $C(R^{5'})(R^{5''})(COOH)$;

$R^{5'}$ and $R^{5''}$ are each independently selected from H, O, S and F; or $R^{5'}$ and $R^{5''}$ together form an O or S;

R^8 and R^9 are each independently selected from H, a halogen, a methyl optionally substituted with one or more halogens, and null; or R^8 and R^9 taken together with Y form a three to five-membered optionally substituted carbocyclic ring;

R^{12} and R^{13} are each independently a C_1-C_3 alkyl optionally substituted with one or more halogens, a C_2-C_3alkenyl optionally substituted with one or more halogens, or a C_2-C_3 akynyl optionally substituted with one or more halogens; or R^{12} and R^{13} taken together with the nitrogen atom to which they are both bound form a five to six-membered heterocyclic ring;

R^{14} and R^{15} are each independently a C_1-C_2 alkyl optionally substituted with one or more halogens, a C_2 alkenyl optionally substituted with one or more halogens, or a C_2 akynyl optionally substituted with one or more halogens;

R^{19} is selected from a halogen, a C_1-C_4 alkyl optionally substituted with one or more fluorines, a C_2-C_4 alkenyl optionally substituted with one or more fluorines, a C_2-C_4 akynyl optionally substituted with one or more fluorines, a C_1-C_4 alkoxy optionally substituted with one or more halogens, a C_1-C_3 thioalkyl optionally substituted with one or more halogens, a C_2-C_3 thioalkenyl optionally substituted with one or more halogens, a C_2-C_3 thioakynyl optionally substituted with one or more halogens , a formyl and a nitro;

R^{20} is selected from a C_4-C_5 alkyl optionally substituted with one or more halogens a C_4-C_5 alkenyl optionally substituted with one or more halogens, a C_4-C_5 akynyl optionally substituted with one or more halogens, a phenyl optionally substituted with one or more fluorines, a thienyl optionally substituted with one or more fluorines, and a benzyl optionally substituted with one or more R^{19};

Y is selected from O, S, N, and C; and

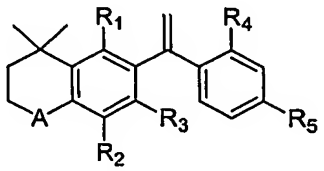
Z is selected from CH_2, NH, and phenylene;

wherein:

if Y is O or S, then each of R^8 and R^9 is null; and

if Y is N, then one of R^8 and R^9 is null.

[011] In certain embodiments, the invention provides a compound of formula VI:



VI

or a pharmaceutically acceptable salt, ester, amide, or prodrug thereof,

wherein:

R^1 is selected from H, a halogen, SH, and OH;

R^2 is selected from H, a halogen, a $NR^{12}R^{13}$, a sulfonamide, a nitro, a formyl, an acyl optionally substituted with one or more halogens, a C_1-C_3 alkyl optionally substituted with one or more fluorines, a C_2-C_3 alkenyl optionally substituted with one or more fluorines, a C_2-C_3 akynyl optionally substituted with one or more fluorines, a C_1-C_2 alkoxy optionally substituted with one or more fluorines, a C_1-C_2 thioalkyl optionally substituted with one or more fluorines, a C_2 thioalkenyl optionally substituted with one or more fluorines, a C_2 thioakynyl optionally substituted with one or more fluorines, and a hydroxylamine optionally substituted with a C_1-C_2 alkyl, a C_2 alkenyl, a C_2 akynyl, a C_1-C_2 fluoroalkyl, a C_2 fluoroalkenyl, or a C_2 fluoroakynyl;

R^3 is selected from H, a halogen, a nitro, a C_1-C_{10} alkyl optionally substituted with one or more halogens, a C_2-C_{10} alkenyl optionally substituted with one or more halogens, a C_2-C_{10} akynyl optionally substituted with one or more halogens, a C_1-C_{10} alkoxy optionally substituted with one or more halogens, a C_1-C_{10} thioalkyl optionally substituted with one or more halogens a C_2-C_{10} thioalkenyl optionally substituted with one or more halogens, a C_2-C_{10} thioakynyl optionally substituted with one or more halogens, a $NR^{14}R^{15}$, and a five to six-membered carbocyclic or heterocyclic ring optionally substituted with up to two R^{19} groups;

R^4 is selected from H, a halogen, and OH;

R^5 is selected from CH_2OH, CHO, COOH, and a $C(R^{5'})(R^{5''})(COOH)$;

$R^{5'}$ and $R^{5''}$ are each independently selected from H, O, S and F; or $R^{5'}$ and $R^{5''}$ together form an O or S;

R^{12} and R^{13} are each independently a C_1-C_3 alkyl optionally substituted with one or more halogens; a C_2-C_3 alkenyl optionally substituted with one or more halogens, or a C_2-C_3 akynyl optionally substituted with one or more halogens; or R^{12} and R^{13} taken together with the nitrogen atom to which they are both bound form a five to six-membered heterocyclic ring;

R^{14} and R^{15} are each independently a C_1-C_2 alkyl optionally substituted with one or more halogens, a C_2 alkenyl optionally substituted with one or more halogens, or C_2 akynyl optionally substituted with one or more halogens;

R^{19} is selected from a halogen, a C_1-C_4 alkyl optionally substituted with one or more fluorines, a C_2-C_4 alkenyl optionally substituted with one or more fluorines, a C_2-C_4 akynyl optionally substituted with one or more fluorines, a C_1-C_4 alkoxy optionally substituted with one or more halogens, a C_1-C_3 thioalkyl optionally substituted with one or more halogens, a C_2-C_3 thioalkenyl optionally substituted with one or more halogens, a C_2-C_3 thioakynyl optionally substituted with one or more halogens, a formyl and a nitro; and

A is selected from O, CH_2, CF_2, and S.

[012] In certain embodiments, the invention provides a pharmaceutical agent comprising a pharmaceutically acceptable carrier and a compound of Formula I, Formula II, Formula III, Formula IV, Formula V, and/or Formula VI.

[013] In certain embodiments, the invention provides a method of treating a patient comprising administering to said patient a pharmaceutical agent comprising a pharmaceutically acceptable carrier and a pharmaceutically effective amount of a compound of Formula I, Formula II, Formula III, Formula IV, Formula V, and/or Formula VI.

[014] In certain embodiments, the invention provides a selective HNF-4α modulator of Formula I, Formula II, Formula III, Formula IV, Formula V, and/or Formula VI. In certain embodiments, the invention provides an HNF-4α selective binding agent of Formula I, Formula II, Formula III, Formula IV, Formula V, and/or Formula VI.

DETAILED DESCRIPTION OF THE INVENTION

[015] It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention claimed. As used herein, the use of the singular includes the plural unless specifically stated otherwise. As used herein, "or" means "and/or" unless stated otherwise. Furthermore, use of the term "including" as well as other forms, such as "includes," and "included," is not limiting.

[016] The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described. All documents, or portions of documents, cited in the application including, but not limited to, patents, patent applications, articles, books, manuals, and treatises are hereby expressly incorporated by reference in their entirety for any purpose.

Definitions

[017] Unless specific definitions are provided, the nomenclatures utilized in connection with, and the laboratory procedures and techniques of, analytical chemistry, synthetic organic chemistry, medicinal chemistry and pharmaceutical chemistry described herein are those known in the art. Standard chemical symbols are used interchangeably with the full names represented by such symbols. Thus, for example, the terms "hydrogen" and "H" are understood to have identical meaning. Standard techniques may be used for chemical syntheses, chemical analyses, pharmaceutical preparation, formulation, delivery, and treatment of patients. Standard techniques may be used for recombinant DNA methodology, oligonucleotide synthesis, tissue culture and transformation (*e.g.*, electroporation, lipofection). Reactions and purification techniques

may be performed *e.g.*, using kits according to manufacturer's specifications, as commonly accomplished in the art or as described herein. The foregoing techniques and procedures may be generally performed according to conventional methods well known in the art and as described in various general or more specific references that are cited and discussed throughout the present specification. *See e.g.*, Sambrook *et al. Molecular Cloning: A Laboratory Manual* (2d ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (1989)), which is incorporated herein by reference for any purpose.

[018] As used herein, the following terms are defined with the following meanings:

[019] The term "selective binding compound" refers to a compound that selectively binds to any portion of one or more target receptors.

[020] The term "selective HNF-4α receptor binding compound" refers to a compound that selectively binds to any portion of an HNF-4α receptor.

[021] The term "selectively binds" refers to the ability of a selective binding compound to bind to a target receptor with greater affinity than it binds to a non-target receptor. In certain embodiments, selective binding refers to binding to a target with an affinity that is at least 10, 50, 100, 250, 500, or 1000 times greater than the affinity for a non-target.

[022] The term "target receptor" refers to a receptor or a portion of a receptor capable of being bound by a selective binding compound. In certain embodiments, a target receptor is an HNF-4α receptor.

[023] The term "modulator" refers to a compound that alters or elicits an activity of a molecule. For example, a modulator may cause an increase or decrease in the magnitude of a certain activity of a molecule compared to the magnitude of the

activity in the absence of the modulator. In certain embodiments, a modulator is an inhibitor, which decreases the magnitude of one or more activities of a molecule. In certain embodiments, an inhibitor completely prevents one or more activities of a molecule. In certain embodiments, a modulator is an activator, which increases the magnitude of at least one activity of a molecule. In certain embodiments the presence of a modulator results in an activity that does not occur in the absence of the modulator.

[024] The term "selective modulator" refers to a compound that selectively modulates a target activity.

[025] The term "selective HNF-4 α receptor modulator" refers to a compound that selectively modulates at least one activity associated with an HNF-4a receptor.

[026] The term "selectively modulates" refers to the ability of a selective modulator to modulate a target activity to a greater extent than it modulates a non-target activity.

[027] The term "target activity" refers to a biological activity capable of being modulated by a selective modulator. Certain exemplary target activities include, but are not limited to, changes in binding affinity, signal transduction, enzymatic activity, transcription of one or more genes, tumor growth, changes in blood glucose concentration, and inflammation or inflammation-related processes.

[028] The term "receptor-mediated activity" refers to any biological activity that results, either directly or indirectly, from binding of a ligand to a receptor.

[029] The term "agonist" refers to a compound, the presence of which results in a biological activity of a receptor that is the same as the biological activity resulting from the presence of a naturally occurring ligand for the receptor.

[030] The term "partial agonist" refers to a compound the presence of which results in a biological activity of a receptor that is of the same type as that resulting from the presence of a naturally occurring ligand for the receptor, but of a lower magnitude.

[031] The term "antagonist" refers to a compound, the presence of which results in a decrease in the magnitude of a biological activity of a receptor. In certain embodiments, the presence of an antagonist results in complete inhibition of a biological activity of a receptor. The term "alkyl," alone or in combination, refers to an optionally substituted straight-chain or branched-chain alkyl radical having from 1 to about 12 carbon atoms. The term also includes substituted straight-chain or branched-chain alkyl radicals having from 1 to about 6 carbon atoms as well as those having from 1 to about 4 carbon atoms. Examples of alkyl radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, tert-amyl, pentyl, hexyl, heptyl, octyl and the like.

[032] The term "alkenyl," alone or in combination, refers to an optionally substituted straight-chain or branched-chain hydrocarbon radical having one or more carbon-carbon double-bonds and having from 2 to about 18 carbon atoms. The term also includes substituted straight-chain or branched-chain alkyl radicals having one or more carbon-carbon double bonds and having from 2 to about 6 carbon atoms as well as those having from 2 to about 4 carbon atoms. Examples of alkenyl radicals include ethenyl, propenyl, 1,4-butadienyl and the like.

[033] The term "alkynyl," alone or in combination, refers to an optionally substituted straight-chain or branched-chain hydrocarbon radical having one or more carbon-carbon triple-bonds and having from 2 to about 12 carbon atoms. The term also includes substituted straight-chain or branched-chain alkyl radicals having one or more carbon-carbon tyriple bonds and having from 2 to about 6 carbon atoms as well as those

having from 2 to about 4 carbon atoms. Examples of alkynyl radicals include ethynyl, propynyl, butynyl and the like.

[034] In certain embodiments, an alkyl comprises 1 to 20 carbon atoms (whenever it appears herein, a numerical range such as "1 to 20" refers to each integer in the given range; *e.g.*, "1 to 20 carbon atoms" means that an alkyl group may comprise only 1 carbon atom, 2 carbon atoms, 3 carbon atoms, etc., up to and including 20 carbon atoms, although the term "alkyl" also includes instances where no numerical range of carbon atoms is designated).

[035] The term "lower alkyl" refers to an alkyl comprising 1 to 6 carbon atoms. The term "medium alkyl" refers to an alkyl comprising 7 to 12 carbon atoms. An alkyl may be designated as "C_1-C_4 alkyl" or similar designations. By way of example only, "C_1-C_4 alkyl", "C_1-C_4 alkenyl" and"C_1-C_4 alkynyl" indicate a radical having one, two, three, or four carbon atoms (*e.g.*, methyl, ethyl, propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, t-butyl, ethenyl, propenyl, butenyl, ethynyl, propynyl, and butynyl).

[036] The term "haloalkyl" refers to an alkyl in which at least one hydrogen atom is replaced with a halogen atom. In certain of the embodiments in which two or more hydrogen atom are replaced with halogen atoms, the halogen atoms are all the same as each other. In certain of such embodiments, the halogen atoms are not all the same as each other.

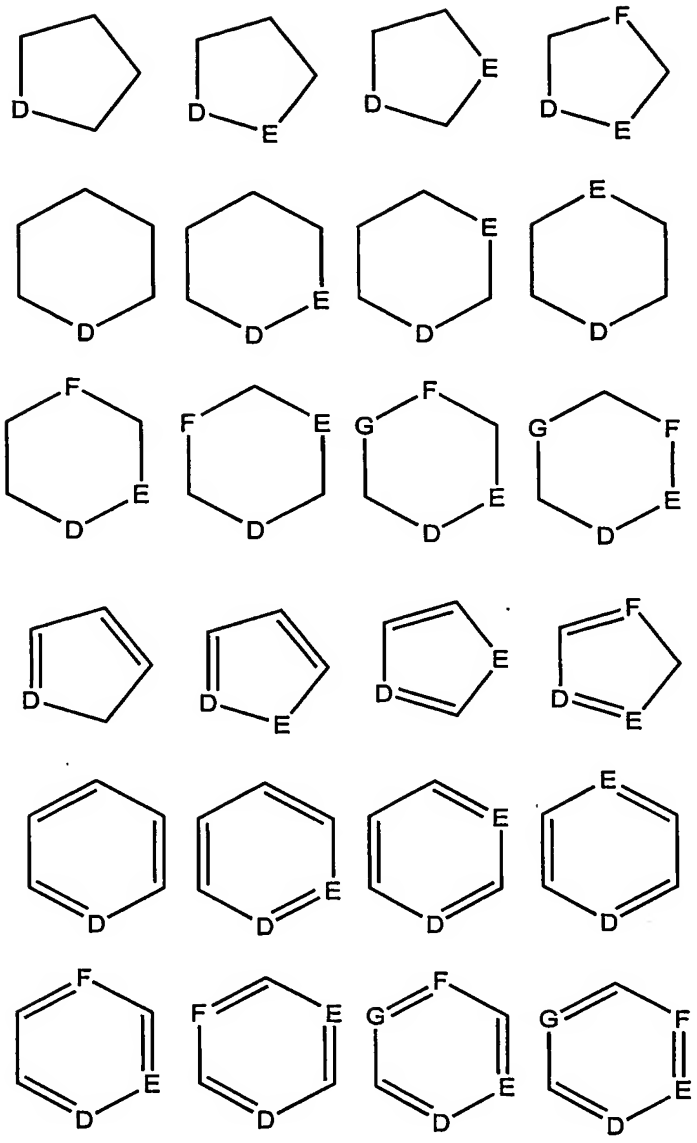
[037] The term "heteroalkyl" refers to a group comprising an alkyl and one or more heteroatoms. Certain heteroalkyls are acylalkyls, in which the one or more heteroatoms are within an alkyl chain. Examples of heteroalkyls, heteroalkenyl, and heteroalkynyls include, but are not limited to, $CH_3C(=O)CH_2$-, $CH_3C(=O)CH_2CH_2$-,

$CH_3CH_2C(=O)CH_2CH_2$-, $CH_3C(=O)CH_2CH_2CH_2$-, $CH_3OCH_2CH_2$-, CH_3NHCH_2-, and the like.

[038] The term "heterohaloalkyl" refers to a heteroalkyl in which at least one hydrogen atom is replaced with a halogen atom.

[039] The term "carbocycle" refers to a group comprising a covalently closed ring, wherein each of the atoms forming the ring is a carbon atom. Carbocyclic rings may be formed by three, four, five, six, seven, eight, nine, or more than nine carbon atoms. Carbocycles may be optionally substituted.

[040] The term "heterocycle" refers to a group comprising a covalently closed ring wherein at least one atom forming the ring is a heteroatom. Heterocyclic rings may be formed by three, four, five, six, seven, eight, nine, or more than nine atoms. Any number of those atoms may be heteroatoms (*i.e.*, a heterocyclic ring may comprise one, two, three, four, five, six, seven, eight, nine, or more than nine heteroatoms). In heterocyclic rings comprising two or more heteroatoms, those two or more heteroatoms may be the same as or different from each other. Heterocycles may be optionally substituted. Binding to a heterocycle can be at a heteroatom or via a carbon atom. For example, binding for benzo-fused derivatives, may be via a carbon of the benzenoid ring. Examples of heterocycles include, but are not limited to the following: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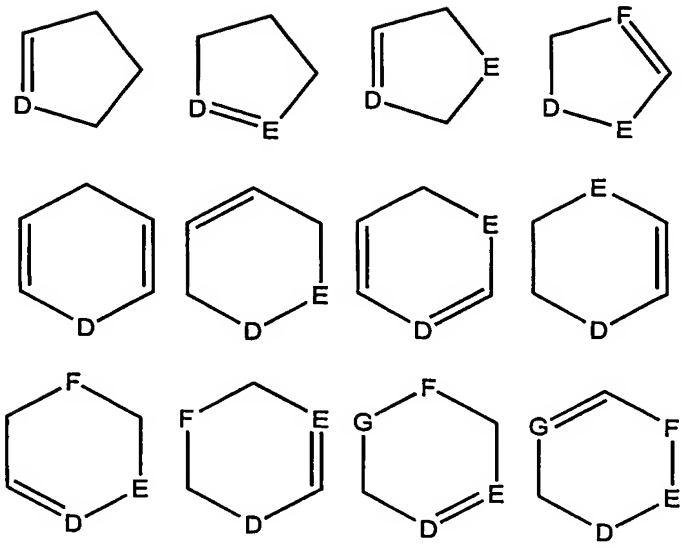


wherein D, E, F, and G each independently represent a heteroatom. Each of D, E, F, and G may be the same as or different from each other.

[041] The term "heteroatom" refers to an atom other than carbon or hydrogen. Heteroatoms are typically independently selected from oxygen, sulfur, nitrogen, and phosphorus, but are not limited to those atoms. In embodiments in which two or more heteroatoms are present, the two or more heteroatoms may all be the same, or some or all of the two or more heteroatoms may each be different from the others.

[042] The term "aromatic" refers to a group comprising a covalently closed ring having a delocalized π-electron system. Aromatic rings may be formed by five, six, seven, eight, nine, or more than nine atoms. Aromatics may be optionally substituted. Examples of aromatic groups include, but are not limited to phenyl, naphthalenyl, phenanthrenyl, anthracenyl, tetralinyl, fluorenyl, indenyl, and indanyl. The term aromatic includes, for example, benzenoid groups, connected via one of the ring-forming carbon atoms, and optionally carrying one or more substituents selected from an aryl, a

heteroaryl, a cycloalkyl, a non-aromatic heterocycle, a halo, a hydroxy, an amino, a cyano, a nitro, an alkylamido, an acyl, a C_{1-6} alkoxy, a C_{1-6} alkyl, a C_{1-6} hydroxyalkyl, a C_{1-6} aminoalkyl, a C_{1-6} alkylamino, an alkylsulfenyl, an alkylsulfinyl, an alkylsulfonyl, an sulfamoyl, and a trifluoromethyl. In certain embodiments, an aromatic group is substituted at one or more of the para, meta, and/or ortho positions. Examples of aromatic groups comprising substitutions include, but are not limited to, phenyl, 3-halophenyl, 4-halophenyl, 3-hydroxyphenyl, 4-hydroxyphenyl, 3-aminophenyl, 4-aminophenyl, 3-methylphenyl, 4-methylphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 4-trifluoromethoxyphenyl, 3-cyanophenyl, 4-cyanophenyl, dimethylphenyl, naphthyl, hydroxynaphthyl, hydroxymethylphenyl, (trifluoromethyl)phenyl, alkoxyphenyl, 4-morpholin-4-ylphenyl, 4-pyrrolidin-1-ylphenyl, 4-pyrazolylphenyl, 4-triazolylphenyl, and 4-(2-oxopyrrolidin-1-yl)phenyl.

[043] The term "aryl" refers to an aromatic group wherein each of the atoms forming the ring is a carbon atom. Aryl rings may be formed by five, six, seven, eight, nine, or more than nine carbon atoms. Aryl groups may be optionally substituted.

[044] The term "heteroaryl" refers to an aromatic group wherein at least one atom forming the aromatic ring is a heteroatom. Heteroaryl rings may be formed by three, four, five, six, seven, eight, nine, or more than nine atoms. Heteroaryl groups may be optionally substituted. Examples of heteroaryl groups include, but are not limited to, aromatic C_{3-8} heterocyclic groups comprising one oxygen or sulfur atom or up to four nitrogen atoms, or a combination of one oxygen or sulfur atom and up to two nitrogen atoms, and their substituted as well as benzo- and pyrido-fused derivatives, for example, connected via one of the ring-forming carbon atoms. In certain embodiments, heteroaryl groups are optionally substituted with one or more substituents, independently selected

from halo, hydroxy, amino, cyano, nitro, alkylamido, acyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} hydroxyalkyl, C_{1-6} aminoalkyl, C_{1-6} alkylamino, alkylsulfenyl, alkylsulfinyl, alkylsulfonyl, sulfamoyl, and trifluoromethyl. Examples of heteroaryl groups include, but are not limited to, unsubstituted and mono- or di-substituted derivatives of furan, benzofuran, thiophene, benzothiophene, pyrrole, pyridine, indole, oxazole, benzoxazole, isoxazole, benzisoxazole, thiazole, benzothiazole, isothiazole, imidazole, benzimidazole, pyrazole, indazole, tetrazole, quinoline, isoquinoline, pyridazine, pyrimidine, purine and pyrazine, furazan, 1,2,3-oxadiazole, 1,2,3-thiadiazole, 1,2,4-thiadiazole, triazole, benzotriazole, pteridine, phenoxazole, oxadiazole, benzopyrazole, quinolizine, cinnoline, phthalazine, quinazoline, and quinoxaline. In some embodiments, the substituents are halo, hydroxy, cyano, O-C_{1-6} alkyl, C_{1-6} alkyl, hydroxy-C_{1-6} alkyl, or amino-C_{1-6} alkyl.

[045] The term "non-aromatic ring" refers to a group comprising a covalently closed ring that does not have a delocalized π-electron system.

[046] The term "cycloalkyl", alone or in combination, refers to a monocyclic, bicyclic or tricyclic alkyl radical wherein each cyclic moiety has from 3 to about 8 carbon atoms. Examples of cycloalkyl radicals include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like.Cycloalkyl rings may be formed by three, four, five, six, seven, eight, nine, or more than nine carbon atoms. Cycloalkyls may be optionally substituted.

[047] The term "non-aromatic heterocycle" refers to a group comprising a non-aromatic ring wherein one or more atoms forming the ring is a heteroatom. Non-aromatic heterocyclic rings may be formed by three, four, five, six, seven, eight, nine, or more than nine atoms. Non-aromatic heterocycles may be optionally substituted. In certain embodiments, non-aromatic heterocycles comprise one or more carbonyl or

thiocarbonyl groups such as, for example, oxo- and thio-containing groups. Examples of non-aromatic heterocycles include, but are not limited to, lactams, lactones, cyclic imides, cyclic thioimides, cyclic carbamates, tetrahydrothiopyran, 4H-pyran, tetrahydropyran, piperidine, 1,3-dioxin, 1,3-dioxane, 1,4-dioxin, 1,4-dioxane, piperazine, 1,3-oxathiane, 1,4-oxathiin, 1,4-oxathiane, tetrahydro-1,4-thiazine, 2H-1,2-oxazine, maleimide, succinimide, barbituric acid, thiobarbituric acid, dioxopiperazine, hydantoin, dihydrouracil, morpholine, trioxane, hexahydro-1,3,5-triazine, tetrahydrothiophene, tetrahydrofuran, pyrroline, pyrrolidine, pyrrolidone, pyrrolidione, pyrazoline, pyrazolidine, imidazoline, imidazolidine, 1,3-dioxole, 1,3-dioxolane, 1,3-dithiole, 1,3-dithiolane, isoxazoline, isoxazolidine, oxazoline, oxazolidine, oxazolidinone, thiazoline, thiazolidine, and 1,3-oxathiolane.

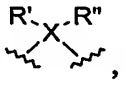
[048] The term "arylalkyl" refers to a group comprising an aryl group bound to an alkyl group.

[049] The term "carbocycloalkyl" refers to a group comprising a carbocyclic cycloalkyl ring. Carbocycloalkyl rings may be formed by three, four, five, six, seven, eight, nine, or more than nine carbon atoms. Carbocycloalkyl groups may be optionally substituted.

[050] The term "ring" refers to any covalently closed structure. Rings include, for example, carbocycles (*e.g.*, aryls and cycloalkyls), heterocycles (*e.g.*, heteroaryls and non-aromatic heterocycles), aromatics (*e.g.*, aryls and heteroaryls), and non-aromatics (*e.g.*, cycloalkyls and non-aromatic heterocycles). Rings may be optionally substituted. Rings may form part of a ring system.

[051] The term "ring system" refers to two or more rings, wherein two or more of the rings are fused. The term "fused" refers to structures in which two or more rings share one or more bonds.

[052] The substituent "R" appearing by itself and without a number designation refers to a substituent selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl (bonded through a ring carbon) and non-aromatic heterocycle (bonded through a ring carbon).

[053] The term "null" refers to a group being absent from a structure. For example, in the structure  , if X is C, then both R' and R" exist, but if X is N, then one of those R groups is null, meaning that only three groups are bound to the N.

[054] The term "O-carboxy" refers to a group of formula RC(=O)O-.

[055] The term "C-carboxy" refers to a group of formula -C(=O)OR.

[056] The term "acetyl" refers to a group of formula $-C(=O)CH_3$.

[057] The term "trihalomethanesulfonyl" refers to a group of formula $X_3CS(=O)_2-$ where X is a halogen.

[058] The term "cyano" refers to a group of formula -CN.

[059] The term "isocyanato" refers to a group of formula -NCO.

[060] The term "thiocyanato" refers to a group of formula -CNS.

[061] The term "isothiocyanato" refers to a group of formula -NCS.

[062] The term "sulfonyl" refers to a group of formula -S(=O)-R.

[063] The term "S-sulfonamido" refers to a group of formula $-S(=O)_2NR$.

[064] The term "N-sulfonamido" refers to a group of formula $RS(=O)_2NH-$.

[065] The term "trihalomethanesulfonamido" refers to a group of formula $X_3CS(=O)_2NR$-.

[066] The term "O-carbamyl" refers to a group of formula -OC(=O)-NR.

[067] The term "N-carbamyl" refers to a group of formula ROC(=O)NH-.

[068] The term "O-thiocarbamyl" refers to a group of formula -OC(=S)-NR.

[069] The term "N-thiocarbamyl" refers to a group of formula ROC(=S)NH-.

[070] The term "C-amido" refers to a group of formula $-C(=O)-NR_2$.

[071] The term "N-amido" refers to a group of formula RC(=O)NH-.

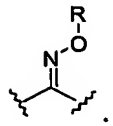
[072] The term "ester" refers to a chemical moiety with formula $-(R)_n$-COOR', where R and R' are independently selected from alkenyl, alkynyl,, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl (bonded through a ring carbon) and non-aromatic heterocycle (bonded through a ring carbon), where n is 0 or 1.

[073] The term "amide" refers to a chemical moiety with formula $-(R)_n$-C(O)NHR' or $-(R)_n$-NHC(O)R', where R and R' are independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl (bonded through a ring carbon) and heteroalicyclic (bonded through a ring carbon), where n is 0 or 1. In certain embodiments, an amide may be an amino acid or a peptide.

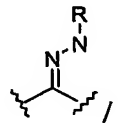
[074] The term "alkoxy," refers to an alkyl ether radical. Examples of alkoxy radicals include, but are not limited to, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy and the like.

[075] The term "formyl" includes aldehydes attached to a compound via an alkyl, aryl, heteroaryl, arylalkyl or heteroarylalkyl group (*e.g.*, -alkyl-CHO, -aryl-CHO, -arylalkyl-CHO or –heteroarylalkyl-CHO, etc.).

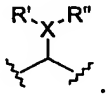
[076] The term "oxime" refers to a group of formula:



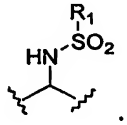
[077] The term "hydrazone" refers to a group of formula:



[078] The term "hydroxylamine" refers to a group of formula:



[079] The term sulfonamide refers to a group of formula:



[080] The term "halogen" includes F, Cl, Br and I

[081] The terms "amine," "hydroxy," and "carboxyl" include such groups that have been esterified or amidified. Procedures and specific groups used to achieve esterification and amidification are known to those of skill in the art and can readily be found in reference sources such as Greene and Wuts, *Protective Groups in Organic*

Synthesis, 3rd Ed., John Wiley & Sons, New York, NY, 1999, which is incorporated by reference herein in its entirety.

[082] Unless otherwise indicated, the term "optionally substituted," refers to a group in which none, one, or more than one of the hydrogen atoms has been replaced with one or more group(s) individually and independently selected from: alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, haloalkyl, haloalkenyl, haloalkynyl, heterohaloalkyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, arylalkyl, heteroaryl, non-aromatic heterocycle, hydroxy, alkoxy, aryloxy, mercapto, alkylthio, alkenylthio, alkynylthio, arylthio, cyano, halo, carbonyl, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, S-sulfonamido, N-sulfonamido, C-carboxy, O-carboxy, isocyanato, thiocyanato, isothiocyanato, nitro, silyl, trihalomethanesulfonyl, and amino, including mono- and di-substituted amino groups, and the protected derivatives of amino groups. Such protective derivatives (and protecting groups that may form such protective derivatives) are known to those of skill in the art and may be found in references such as Greene and Wuts, *supra*. In embodiments in which two or more hydrogen atoms have been substituted, the substituent groups may together form a ring.

[083] The term "carrier" refers to a compound that facilitates the incorporation of another compound into cells or tissues. For example, dimethyl sulfoxide (DMSO) is a commonly used carrier for improving incorporation of certain organic compounds into cells or tissues.

[084] The term "pharmaceutical agent" refers to a chemical compound or composition capable of inducing a desired therapeutic effect in a patient. In certain embodiments, a pharmaceutical agent comprises an active agent, which is the agent that

induces the desired therapeutic effect. In certain embodiments, a pharmaceutical agent comprises a prodrug. In certain embodiments, a pharmaceutical agent comprises inactive ingredients such as carriers, excipients, and the like.

[085] The term "therapeutically effective amount" refers to an amount of a pharmaceutical agent sufficient to achieve a desired therapeutic effect.

[086] The term "prodrug" refers to a pharmaceutical agent that is converted from a less active form into a corresponding more active form *in vivo*.

[087] The term "pharmaceutically acceptable" refers to a formulation of a compound that does not significantly abrogate a biological activity, a pharmacological activity and/or other properties of the compound when the formulated compound is administered to a patient. In certain embodiments, a pharmaceutically acceptable formulation does not cause significant irritation to a patient.

[088] The term "co-administer" refers to administering more than one pharmaceutical agent to a patient. In certain embodiments, co-administered pharmaceutical agents are administered together in a single dosage unit. In certain embodiments, co-administered pharmaceutical agents are administered separately. In certain embodiments, co-administered pharmaceutical agents are administered at the same time. In certain embodiments, co-administered pharmaceutical agents are administered at different times.

[089] The term "patient" includes human and animal subjects.

[090] The term "substantially pure" means an object species (*e.g.*, compound) is the predominant species present (*i.e.*, on a molar basis it is more abundant than any other individual species in the composition). In certain embodiments, a substantially pure composition is a composition wherein the object species comprises at least about 50

percent (on a molar basis) of all species present. In certain embodiments, a substantially pure composition is a composition wherein the object species comprises more than about 80%, 85%, 90%, 95%, or 99% of all species present in the composition. In certain embodiments, a substantially pure object species is purified to essential homogeneity (contaminant species cannot be detected in the composition by conventional detection methods) wherein the composition consists essentially of the single object species.

[091] The term "tissue-selective" refers to the ability of a compound to modulate a biological activity in one tissue to a greater or lesser degree than it modulates a biological activity in another tissue. The biological activities modulated in the different tissues may be the same or they may be different. The biological activities modulated in the different tissues may be mediated by the same type of target receptor. For example, in certain embodiments, a tissue-selective compound may modulate an HNF-4α receptor-mediated biological activity in one tissue and fail to modulate, or modulate to a lesser degree, an HNF-4α receptor-mediated biological activity in another tissue type.

[092] The term "monitoring" refers to observing an effect or absence of any effect. In certain embodiments, cells are monitored after contacting those cells with a compound of the present invention. Examples of effects that may be monitored include, but are not limited to, changes in cell phenotype, cell proliferation, an HNF-4α receptor activity, or the interaction between an HNF-4α receptor and a natural binding partner.

[093] The term "cell phenotype" refers to physical or biological characteristics. Examples of characteristics that constitute phenotype included, but are not limited to, cell size, cell proliferation, cell differentiation, cell survival, apoptosis (cell death), or the

utilization of a metabolic nutrient (*e.g.*, glucose uptake). Certain changes or the absence of changes in cell phenotype are readily monitored using techniques known in the art.

[094] The term "cell proliferation" refers to the rate at which cells divide. The number of cells growing in a vessel can be quantified by a person skilled in the art (*e.g.*, by counting cells in a defined area using a light microscope, or by using laboratory apparatus that measure the density of cells in an appropriate medium). One skilled in that art can calculate cell proliferation by determining the number of cells in a sample at two or more times.

[095] The term "contacting" refers to bringing two or more materials into close enough proximity that they may interact. In certain embodiments, contacting can be accomplished in a vessel such as a test tube, a petri dish, or the like. In certain embodiments, contacting may be performed in the presence of additional materials. In certain embodiments, contacting may be performed in the presence of cells. In certain of such embodiments, one or more of the materials that are being contacted may be inside a cell. Cells may be alive or may dead. Cells may or may not be intact.

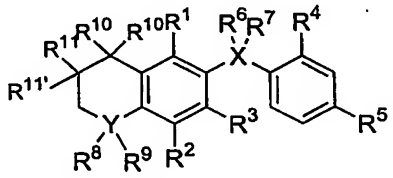
Certain compounds

[096] Certain compounds that bind to HNF-4α receptors and/or certain compounds that modulate an activity of such receptors play a role in health (*e.g.*, normal growth, development, and/or absence of disease). In certain embodiments, compounds of the present invention are useful for treating any of a variety of diseases or conditions.

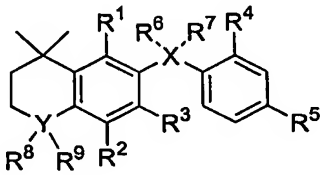
[097] Certain compounds have been previously described as receptor modulators. See *e.g.*, U. S. Patent Nos. 6,462,038, 5,693,646; 6,380,207; 6,506,766; 5,688,810; 5,696,133; 6,569,896, 6,673,799; 4,636,505; 4,097,578; 3,847,988; U.S. Patent Application No. 10/209,461 (Pub. No. US 2003/0055094); International Patent

Application Nos. WO 01/27086 and WO 02/22585; Zhi, *et al. Bioorganic & Med. Chem. Lett.* 2000, **10**:415-418; Pooley, *et al., J. Med. Chem.* 1998, **41**:3461; Hamann, *et al. J. Med. Chem.* 1998, **41**:623; and Yin, *et al., Molec. Pharmacol.*, 2003, **63**:211-223 the entire disclosures of which are incorporated by reference herein in their entirety. Certain cyclothiocarbamate analogues have been described as progesterone receptor modulators (*e.g.*, U.S. Pat. Nos. 6,436,929 and 6,509,334). Certain cyclocarbamate analogues have been described as progesterone receptor antagonists (*e.g.*, U.S. Pat. Nos. 6,306,851, 6,380,178, 6,441,019, 6,444,668, 6,509,334, and 6,566,358; Zhang, *et al. J. Med. Chem.* **45**:4379 (2002)).

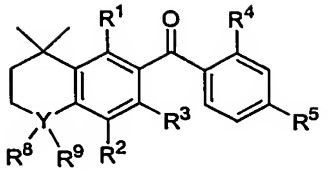
[098] In certain embodiments, the invention provides a compound of formula I, II, III, IV, V, or VI:



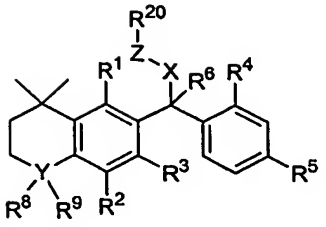
I



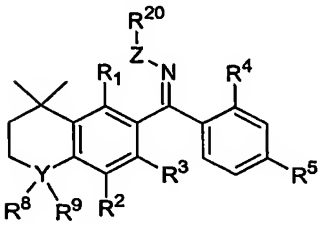
II



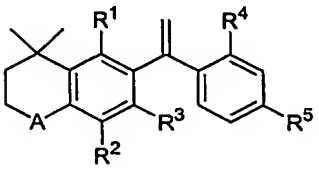
III



IV



V



VI

or a pharmaceutically acceptable sale, ester, amide, or prodrug thereof.

[099] In certain embodiments, R^1 is selected from H, a halogen, SH, and OH.

[0100] In certain embodiments, R^2 is selected from H, a halogen, an optionally substituted C_1–C_6 alkyl, an optionally substituted C_2-C_6 alkenyl, an optionally substituted C_2-C_6 akynyl, an optionally substituted C_1-C_6 heteroalkyl, an optionally substituted C_2-C_6 heteroalkenyl, an optionally substituted C_2-C_6 heteroakynyl, an optionally substituted C_1-C_6 haloalkyl, an optionally substituted C_2-C_6 haloalkenyl, an optionally substituted C_2-C_6 haloakynyl, an optionally substituted C_1-C_6 heterohaloalkyl, an optionally substituted C_2-C_6 heterohaloalkenyl, an optionally substituted C_2-C_6 heterohaloakynyl, an optionally substituted C_3–C_8 cycloalkyl, an optionally substituted C_3-C_8 cycloalkenyl, an optionally substituted C_3-C_8 cycloakynyl, an optionally substituted C_3–C_8 heterocycle, an optionally substituted C_3–C_8 aryl, an optionally substituted C_3–C_8 heteroaryl, an optionally substituted C_1-C_2 alkoxy, a $NR^{12}R^{13}$, an optionally substituted sulfonamide, an optionally substituted C_1-C_2 thioalkyl, an optionally substituted C_2 thioalkenyl, an

optionally substituted C_2 thioakynyl, an optionally substituted nitro, an optionally substituted formyl, an optionally substituted acyl, and an optionally substituted hydroxylamine. In certain embodiments, R^2 is an optionally substituted C_1-C_8 alkyl, an optionally substituted C_2-C_8 alkenyl, an optionally substituted C_2-C_8 akynyl, an optionally substituted C_2-C_8 thioalkyl, an optionally substituted C_2-C_8 thioalkenyl, an optionally substituted C_2-C_8 thioakynyl, or an optionally substituted C_3–C_8 cycloalkyl. In certain embodiments, R^2 is an optionally substituted C_1-C_8 alkyl, an optionally substituted C_2-C_8 alkenyl, an optionally substituted C_2-C_8 akynyl, an optionally substituted C_2-C_8 thioalkyl, an optionally substituted C_2-C_8 thioalkenyl, an optionally substituted C_2-C_8 thioakynyl, an optionally substituted C_3–C_8 cycloalkyl, an optionally substituted C_3-C_8 cycloalkenyl, or an optionally substituted C_3-C_8 cycloakynyl. In certain of such embodiments, R^2 is selected from an optionally substituted C_2-C_8 alkenyl, an optionally substituted C_2-C_8 alkynyl, an optionally substituted C_2-C_3 thioalkenyl, an optionally substituted C_2-C_3 thioalkynyl, an optionally substituted C_3-C_8 cycloalkenyl, and an optionally substituted C_3-C_8 cycloalkynyl. In certain embodiments, R^2 is selected from an optionally substituted methyl, ethyl propyl isopropyl, butyl, sec-butyl, and tert-butyl. In certain of the embodiments where R^2 is a halogen, R^2 is F or Cl. In certain embodiments where R^2 is selected from an optionally substituted alkyl, alkenyl, alkynyl, alkoxy, thioalkyl, thioalkenyl, thioalkynyl, aldehyde and ketone, those groups are optionally substituted with one or more fluorines. In certain embodiments where R^2 is selected from an optionally substituted hydroxylamine, that group is optionally substituted with a C_1-C_2 alkyl, a C_2 alkenyl, a C_2 akynyl, a C_1-C_2 fluoroalkyl, a C_2 a fluoroalkenyl, or a C_2 fluoroakynyl,.

[0101] In certain embodiments, R^3 is selected from H, a halogen, a nitro, an optionally substituted C_1-C_{10} alkyl, an optionally substituted C_2-C_{10} alkenyl, an optionally substituted C_2-C_{10} akynyl, an optionally substituted C_1-C_{10} alkoxy, an optionally substituted C_1-C_{10} thioalkyl, an optionally substituted C_2-C_{10} thioalkenyl, an optionally substituted C_2-C_{10} thioakynyl, a $NR^{14}R^{15}$, and an optionally substituted five to six-membered carbocyclic or heterocyclic ring. In certain embodiments, R^3 is an optionally substituted C_1-C_8 alkyl, an optionally substituted C_2-C_8 alkenyl, an optionally substituted C_2-C_8 akynyl, an optionally substituted C_2-C_8 thioalkyl, an optionally substituted C_2-C_8 thioalkenyl, an optionally substituted C_2-C_8 thioakynyl, or an optionally substituted C_3–C_8 cycloalkyl. In certain embodiments, R^3 is an optionally substituted C_1-C_8 alkyl, an optionally substituted C_2-C_8 alkenyl, an optionally substituted C_2-C_8 akynyl, an optionally substituted C_2-C_8 thioalkyl, an optionally substituted C_2-C_8 thioalkenyl, an optionally substituted C_2-C_8 thioakynyl, an optionally substituted C_3–C_8 cycloalkyl, an optionally substituted C_3-C_8 cycloalkenyl, or an optionally substituted C_3-C_8 cycloakynyl. In certain of suchembodiments, R^3 is selected from an optionally substituted C_2-C_8 alkenyl, an optionally substituted C_2-C_8 alkynyl, an optionally substituted C_2-C_3 thioalkenyl, an optionally substituted C_2-C_3 thioalkynyl, an optionally substituted C_3-C_8 cycloalkenyl, and an optionally substituted C_3-C_8 cycloalkynyl. In certain embodiments, R^3 is selected from an optionally substituted methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, and tert-butyl. In certain of the embodiments where R^3 is a halogen, R_3 is F or Cl. In certain embodiments where R^3 is selected from an optionally substituted alkyl, alkenyl, alkynyl, alkoxy, thioalkyl, thioalkenyl, thioalkynyl, aldehyde and ketone, those groups are optionally substituted with one or more halogens. In

certain embodiments where R^3 is selected from an optionally substituted carboxylic or heterocyclic ring, that ring is optionally substituted with a one or two R^{19} groups.

[0102] In certain embodiments, R^4 is selected from H, a halogen, and OH.

[0103] In certain embodiments, R^5 is selected from CH_2OH, CHO, COOH, and a $C(R^{5'})(R^{5''})(COOH)$.

[0104] In certain embodiments, $R^{5'}$ and $R^{5''}$ are each independently selected from H, O, S and F. In certain embodiments, $R^{5'}$ and $R^{5''}$ together are O or S.

[0105] In certain embodiments, R^6 and R^7 are each independently selected from H, a halogen, a $NHC(O)R^{18}$, an optionally substituted C_1–C_6 alkyl, an optionally substituted C_2-C_6 alkenyl, an optionally substituted C_2-C_6 akynyl, an optionally substituted C_2-C_6 alkenyl, C_1-C_6 heteroalkyl, an optionally substituted C_2-C_6 heteroalkenyl, an optionally substituted C_2-C_6 heteroakynyl, an optionally substituted C_1-C_6 haloalkyl, an optionally substituted C_2-C_6 haloalkenyl, an optionally substituted C_2-C_6 haloakynyl, an optionally substituted C_1-C_6 heterohaloalkyl, an optionally substituted C_2-C_6 heterohaloalkenyl, an optionally substituted C_2-C_6 heterohaloakynyl, an optionally substituted C_3–C_8 cycloalkyl, an optionally substituted C_3-C_8 cycloalkenyl, an optionally substituted C_3-C_8 cycloakynyl, an optionally substituted C_3–C_8 heterocycle, an optionally substituted C_3–C_8 aryl, an optionally substituted C_3–C_8 heteroaryl, an optionally substituted C_1-C_2 alkoxy, a $NR^{12}R^{13}$, an optionally substituted sulfonamide, an optionally substituted C_1-C_2 thioalkyl, an optionally substituted C_2 thioalkenyl, an optionally substituted C_2 thioakynyl, an optionally substituted nitro, an optionally substituted formyl, an optionally substituted acyl, an optionally substituted hydroxylamine, and null. In certain embodiments, R^6 and/or R^7 is an optionally substituted C_1-C_8 alkyl, an optionally substituted C_2-C_8 alkenyl, an optionally substituted C_2-C_8 akynyl, an

optionally substituted C_2-C_8 thioalkyl, an optionally substituted C_2-C_8 thioalkenyl, an optionally substituted C_2-C_8 thioakynyl, or an optionally substituted C_3–C_8 cycloalkyl. In certain embodiments, R^6 and/or R^7 is an optionally substituted C_1-C_8 alkyl, an optionally substituted C_2-C_8 alkenyl, an optionally substituted C_2-C_8 akynyl, an optionally substituted C_2-C_8 thioalkyl, an optionally substituted C_2-C_8 thioalkenyl, an optionally substituted C_2-C_8 thioakynyl, or an optionally substituted C_3–C_8 cycloalkyl, an optionally substituted C_3-C_8 cycloalkenyl,or an optionally substituted C_3-C_8 cycloakynyl . In certain of such embodiments, R^6 and/or R^7 is selected from an optionally substituted C_2-C_8 alkenyl, an optionally substituted C_2-C_8 alkynyl, an optionally substituted C_2-C_3 thioalkenyl, an optionally substituted C_2-C_3 thioalkynyl, an optionally substituted C_3-C_8 cycloalkenyl, and an optionally substituted C_3-C_8 cycloalkynyl. In certain embodiments, R^6 and/or R^7 is selected from an optionally substituted methyl, ethyl propyl isopropyl, butyl, sec-butyl, and tert-butyl. In certain of the embodiments where R^6 and/or R^7 is a halogen, R^6 and/or R^7 is F or Cl. In certain embodiments where R^6 and/or R^7 is selected from an optionally substituted alkyl, alkenyl, alkynyl, alkoxy, thioalkyl, thioalkenyl, thioalkynyl, aldehyde and ketone, those groups are optionally substituted with one or more fluorines. In certain embodiments where R^6 and/or R^7 is selected from an optionally substituted hydroxylamine, that hydroxylamine is optionally substituted with a C_1-C_2 alkyl, a C_2 alkenyl, a C_2 akynyl, a C_1-C_2 fluoroalkyl, a C_2 fluoroalkenyl, or a C_2 fluoroakynyl,.

[0106] In certain embodiments, R^6 and R^7 taken together form a group selected from O, S, NH and CH_2.

[0107] In certain embodiments, R^8 and R^9 are each independently selected from H, a halogen, an optionally substituted C_1-C_2 alkyl, an optionally substituted C_2 alkenyl,

an optionally substituted C_2 akynyl, and null. In certain embodiments, R^8 and/or R^9 is methyl optionally substituted with one or more halogens. In certain embodiments, R^8 and R^9 taken together with Y form a three to five-membered optionally substituted carbocyclic ring.

[0108] In certain embodiments, R^{10} is selected from H, a halogen, an optionally substituted C_1-C_2 alkyl, an optionally substituted C_2 alkenyl, and an optionally substituted C_2 akynyl. In certain embodiments, R^{10} is a methyl optionally substituted with one or more halogens.

[0109] In certain embodiments, R^{11} and $R^{11'}$ are each independently selected from H, a halogen and OH. In certain embodiments, R^{11} and $R^{11'}$ taken together form an O. In certain embodiments, if R^{11} is OH, then $R^{11'}$ is H.

[0110] In certain embodiments, R^{12} and R^{13} are each independently selected from a C_1-C_3 alkyl optionally substituted with one or more halogens, C_2-C_3 alkenyl optionally substituted with one or more halogens, and a C_2-C_3 akynyl optionally substituted with one or more halogens. In certain embodiments, R^{12} and R^{13} taken together with the nitrogen atom to which they are both bound form a five to six-membered optionally substituted heterocyclic ring.

[0111] In certain embodiments, R^{14} and R^{15} are each independently selected from a C_1-C_2 alkyl optionally substituted with one or more halogens, an C_2-C_6 alkenyl optionally substituted with one or more halogens, and a C_2-C_6 akynyl optionally substituted with one or more halogens.

[0112] In certain embodiments, R^{16} and R^{17} are each independently selected from an optionally substituted C_1–C_{12} alkyl, optionally substituted C_2-C_{12} alkenyl, optionally substituted C_2-C_{12} akynyl, an optionally substituted C_1-C_{12} heteroalkyl, an optionally

substituted C_2-C_{12} heteroalkenyl, an optionally substituted C_2-C_{12} akynyl, an optionally substituted C_1-C_{12} haloalkyl, an optionally substituted C_2-C_{12} haloalkenyl, an optionally substituted C_2-C_{12} haloakynyl, an optionally substituted C_1-C_{12} heterohaloalkyl, an optionally substituted C_2-C_{12} heterohaloalkenyl, an optionally substituted C_2-C_{12} heterohaloakynyl, an optionally substituted C_3–C_{12} cycloalkyl, an optionally substituted C_3-C_{12} alkenyl, an optionally substituted C_3-C_{12} akynyl, an optionally substituted C_3–C_{12} heterocycle, an optionally substituted C_3–C_{12} aryl, and an optionally substituted C_3–C_{12} heteroaryl. In certain embodiments, R^{16} and/or R^{17} is an optionally substituted C_1-C_{12} alkyl, optionally substituted C_2-C_{12} alkenyl, optionally substituted C_2-C_{12} akynyl, an optionally substituted C_3–C_{12} cycloalkyl, an optionally substituted C_3-C_{12} cycloalkenyl, or an optionally substituted C_3-C_{12} cycloakynyl. In certain embodiments, R^{16} and/or R^{17} is an optionally substituted C_1-C_{12} alkyl optionally substituted C_2-C_{12} alkenyl, optionally substituted C_2-C_{12} akynyl, an optionally substituted C_3–C_{12} cycloalkyl, an optionally substituted C_3-C_{12} cycloalkenyl, or an optionally substituted C_3-C_{12} cycloakynyl. In certain of such embodiments, R^{16} and/or R^{17} is selected from an optionally substituted C_2-C_{12} alkenyl, an optionally substituted C_2-C_{12} alkynyl, an optionally substituted C_3-C_{12} cycloalkenyl, and an optionally substituted C_3-C_{12} cycloalkynyl. In certain embodiments, R^{16} and/or R^{17} is selected from an optionally substituted methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, and tert-butyl. In certain embodiments where R^{16} and/or R^{17} is optionally substituted with one or more R^{19}.

[0113] In certain embodiments, R^{16} and R^{17} taken together with the nitrogen atom to which they are both bound form a five to six-membered optionally substituted heterocyclic ring.

[0114] In certain embodiments, R^{18} is selected from an optionally substituted C_1–C_{12} alkyl, optionally substituted C_2-C_{12} alkenyl, optionally substituted C_2-C_{12} akynyl, an optionally substituted C_1-C_{12} heteroalkyl, an optionally substituted C_2-C_{12} heteroalkenyl, an optionally substituted C_2-C_{12} heteroakynyl, an optionally substituted C_1-C_{12} haloalkyl, an optionally substituted C_2-C_{12} haloalkenyl, an optionally substituted C_2-C_{12} haloakynyl, an optionally substituted C_1-C_{12} heterohaloalkyl, an optionally substituted C_2-C_{12} heterohaloalkenyl, an optionally substituted C_2-C_{12} heterohaloakynyl, an optionally substituted C_3–C_{12} cycloalkyl, an optionally substituted C_3-C_8 cycloalkenyl, an optionally substituted C_3-C_8 cycloakynyl, an optionally substituted C_3–C_{12} heterocycle, an optionally substituted C_3–C_{12} aryl, and an optionally substituted C_3–C_{12} heteroaryl. In certain embodiments, R^{18} is an optionally substituted C_1-C_{12} alkyl, an optionally substituted C_2-C_{12} alkenyl, an optionally substituted C_2-C_{12} akynyl, or an optionally substituted C_3–C_{12} cycloalkyl . In certain embodiments, R^{18} is an optionally substituted C_1-C_{12} alkyl, optionally substituted C_2-C_{12} alkenyl, optionally substituted C_2-C_{12} akynyl, an optionally substituted C_3–C_{12} cycloalkyl, an optionally substituted C_3-C_{12} cycloalkenyl, or an optionally substituted C_3-C_{12} cycloakynyl . In certain of such embodiments, R^{18} is selected from an optionally substituted C_2-C_{12} alkenyl, an optionally substituted C_2-C_{12} alkynyl, an optionally substituted C_3-C_{12} cycloalkenyl, and an optionally substituted C_3-C_{12} cycloalkynyl. In certain embodiments, R^{18} is selected from an optionally substituted methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, and tert-butyl. In certain embodiments R^{18} is optionally substituted with one or more R^{19}.

[0115] In certain embodiments, R^{19} is selected from a halogen, an optionally substituted C_1-C_4 alkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 akynyl, an optionally substituted C_1-C_4 alkoxy, an optionally substituted C_1-C_3 thioalkyl,

optionally substituted C_2-C_3 thioalkenyl, optionally substituted C_2-C_3 thioakynyl, an optionally substituted formyl, and an optionally substituted nitro. In certain embodiments, R^{19} is a C_1-C_4 alkyl optionally substituted with one or more fluorines, a C_2-C_4 alkenyl optionally substituted with one or more fluorines, or a C_2-C_4 akynyl optionally substituted with one or more fluorines. In certain embodiments, R^{19} is a C_1-C_4 alkoxy optionally substituted with one or more halogens. In certain embodiments, R^{19} is a C_1-C_3 thioalkyl optionally substituted with one or more halogens, a C_2-C_3 thioalkenyl optionally substituted with one or more halogens, or a C_2-C_3 thioakynyl optionally substituted with one or more halogens.

[0116] In certain embodiments, R^{20} is selected from a C_4-C_5 alkyl optionally substituted with one or more halogens, a C_4-C_5 alkenyl optionally substituted with one or more halogens, a C_4-C_5 akynyl optionally substituted with one or more halogens, a phenyl optionally substituted with one or more fluorines, a thienyl optionally substituted with one or more fluorines, and a benzyl optionally substituted with one or more R^{21}.

[0117] In certain embodiments, R^{21} is selected from a halogen, a methyl optionally substituted with one or more fluorines, and a thiomethyl optionally substituted with one or more halogens.

[0118] In certain embodiments, X and Y are each independently selected from O, S, N and C.

[0119] In certain embodiments, A is selected from O, CH_2, CF_2 and S.

[0120] In certain embodiments, Z is selected from C, N and phenylene.

[0121] In certain embodiments, if X is O or S, then each of R^6 and R^7 is null; if X is N, then one of R^6 and R^7 is null; if Y is O or S, then each of the R^8 and R^9 is null; and if Y is N, then one of R^8 and R^9 is null.

[0122] In certain embodiments, if R^6 is selected from a halogen, a C_1-C_{12} alkyl a C_2-C_{12} alkenyl, a C_2-C_{12} alkynyl or a C_2-C_{12} alkoxy any of which is optionally substituted with one or more R^{19}, or a C_1-C_{12} thioalkyl C_1-C_{12} thioalkenyl or C_1-C_{12} thioalkynyl any of which is optionally substituted with one or more R^{19}, $NR^{16}R^{17}$ or $HNC(O)R^{18}$, then R^7 is H or F.

[0123] In certain embodiments, if Y is N then neither R^8 nor R^9 is a halogen.

[0124] In certain embodiments, if R^{19} is selected from a C_1-C_4 alkyl substituted with one or more halogens, a C_2-C_4 alkenyl substituted with one or more halogens, a C_2-C_4 akynyl substituted with one or more halogens, a C_1-C_4 alkoxy group substituted with one or more halogens, a C_1-C_3 thioalkyl substituted with one or more halogens, a C_2-C_3 thioalkenyl substituted with one or more halogens, and C_2-C_3 akynyl substituted with one or more halogens, group substituted with one or more halogens, then each of R^3, R^{16} and R^{17} is substituted with no more than two R^{19} groups.

[0125] In certain embodiments, if R^3 is a methyl substituted with one or more fluorines, then neither R^1 nor R^2 is either hydrogen or a halogen.

[0126] In certain embodiments, if R^4 is a halogen, then R^3 is an ethoxy optionally substituted with one or more fluorines.

[0127] In certain embodiments, if Y is nitrogen then neither R^8 nor R^9 is a halogen. In certain embodiments, if Y is either oxygen or sulfur, then R^8 is null and R^9 is null.

[0128] In embodiments in which two or more of a particular group are present, the identities of those two or more particular groups are selected independently and, thus, may be the same or different from one another. For example, certain compounds of the invention comprise two or more R^{19} groups. The identities of those two or more R^{19}

groups are each selected independently. Thus, in certain embodiments, those R^{19} groups are all the same aseach other; in certain embodiments, those R^{19} groups are all different fromeach other; and in certain embodiments, some of those R^{19} groups are the same as each other and some are different from the others. This independent selection applies to any group that is present in a compound more than once.

[0129] Certain compounds of the present inventions may exist as stereoisomers including, but not limited to, optical isomers. The present disclosure is intended to include all stereoisomers and both the racemic mixtures of such stereoisomers as well as the individual enantiomers that may be separated according to methods that are known in the art or that may be excluded by synthesis schemes known in the art designed to yield predominantly one enantiomer relative to another.

[0130] As used herein, the term "stereoisomer" refers to a compound made up of the same atoms bonded by the same bonds but having different three-dimensional structures which are not interchangeable. The three-dimensional structures are called configurations. As used herein, the term "enantiomer" refers to two stereoisomers whose molecules are nonsuperimposable mirror images of one another. The term "chiral center" refers to a carbon atom to which four different groups are attached. As used herein, the term "diastereomers" refers to stereoisomers which are not enantiomers. In addition, two diastereomers which have a different configuration at only one chiral center are referred to herein as "epimers." The terms "racemate," "racemic mixture" or "racemic modification" refer to a mixture of equal parts of enantiomers.

[0131] The compounds of the present invention may be chiral, and it is intended that any enantiomers, as separated, pure or partially purified enantiomers or racemic mixtures thereof are included within the scope of the invention. Furthermore, when a

double bond or a fully or partially saturated ring system or more than one center of asymmetry or a bond with restricted rotatability is present in the molecule diastereomers may be formed. It is intended that any diastereomers, as separated, pure or partially purified diastereomers or mixtures thereof are included within the scope of the invention. Furthermore, some of the compounds of the present invention may exist in different tautomeric forms and it is intended that any tautomeric forms, which the compounds are able to form, are included within the scope of the present invention. Thus, as one skilled in the art knows, certain aryls may exist in tautomeric forms. The invention also includes tautomers, enantiomers and other stereoisomers of the compounds of Formula I. Such variations are contemplated to be within the scope of the invention.

[0132] The terms "R" and "S" are used herein as commonly used in organic chemistry to denote specific configuration of a chiral center. The term "R" (rectus) refers to that configuration of a chiral center with a clockwise relationship of group priorities (highest to second lowest) when viewed along the bond toward the lowest priority group. The term "S" (sinister) refers to that configuration of a chiral center with a counterclockwise relationship of group priorities (highest to second lowest) when viewed along the bond toward the lowest priority group. The priority of groups is based upon their atomic number (in order of decreasing atomic number). A partial list of priorities and a discussion of stereochemistry is contained in "Nomenclature of Organic Compounds: Principles and Practice", (J.H. Fletcher, et al., eds., 1974) at pages 103-120.

[0133] The designation " " refers to a bond that protrudes forward out of the plane of the page.

[0134] The designation " " refers to a bond that protrudes backward out of the plane of the page.

[0135] The designation " ~~~ " refers to a bond wherein the stereochemistry is not defined.

[0136] The compounds of Formula I, when existing as a diastereomeric mixture, may be separated into diastereomeric pairs of enantiomers by, for example, fractional crystallization from a suitable solvent, for example methanol or ethyl acetate or a mixture thereof. The pair of enantiomers thus obtained may be separated into individual stereoisomers by conventional means, for example by the use of an optically active acid as a resolving agent. Alternatively, any enantiomer of a compound of Formula I may be obtained by stereospecific synthesis using optically pure starting materials or reagents of known configuration or through enantioselective synthesis.

[0137] The term "enantiomeric enrichment" as used herein refers to the increase in the amount of one enantiomer as compared to the other. A convenient method of expressing the enantiomeric enrichment achieved is the concept of enantiomeric excess, or "ee," which is found using the following equation:

$$ee = \frac{E^1 - E^2}{E^1 + E^2} \times 100$$

[0138] wherein E^1 is the amount of the first enantiomer and E^2 is the amount of the second enantiomer. Thus, if the initial ratio of the two enantiomers is 50:50, such as is present in a racemic mixture, and an enantiomeric enrichment sufficient to produce a final ratio of 70:30 is achieved, the ee with respect to the first enantiomer is 40%. However, if the final ratio is 90:10, the ee with respect to the first enantiomer is 80%. An ee of greater than 90% is preferred, an ee of greater than 95% is most preferred and an ee of greater than 99% is most especially preferred. Enantiomeric enrichment is readily determined by one of ordinary skill in the art using standard techniques and

procedures, such as gas or high performance liquid chromatography with a chiral column. Choice of the appropriate chiral column, eluent and conditions necessary to effect separation of the enantiomeric pair is well within the knowledge of one of ordinary skill in the art. In addition, the specific stereoisomers and enantiomers of compounds of Formula I can be prepared by one of ordinary skill in the art utilizing well known techniques and processes, such as those disclosed by J. Jacques, *et al.*, "Enantiomers, Racemates, and Resolutions," John Wiley and Sons, Inc., 1981, and E.L. Eliel and S.H. Wilen," Stereochemistry of Organic Compounds," (Wiley-Interscience 1994), and European Patent Application No. EP-A-838448, published April 29, 1998. Examples of resolutions include recrystallization techniques or chiral chromatography.

[0139] The following table provides examples of certain variables from various Markush groups in this application. One of ordinary skill in the art will recognize that the variables may selected in any combination.

Table A. Table of Markush Groups by Variable

	Markush Group A	Markush Group B	Markush Group C	Markush Group D
R^1	H, halogen, SH, and OH	H, SH and OH	H and OH	H
R^2	H, halogen, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_1-C_3 alkoxy, $NR^{11}R^{12}$, sulfonamide, C_1-C_3 thioalkyl, C_2-C_3 thioalkenyl, C_2-C_3 thioalkynyl, nitro, formyl, acyl, and hydroxylamine, wherein the alkyl, alkenyl, alkynyl, alkoxy, thioalkyl, thioalkenyl, thioalkynyl, aldehyde and ketone groups are optionally substituted with one or more fluorines, and wherein the hydroxylamine group is optionally substituted with a C_1-C_2 alkyl group or a C_1-C_2 fluoroalkyl group;	H, halogen, C_1-C_2 alkyl, C_2-C_3 alkenyl, C_2-C_3 alkynyl, C_1-C_2 alkoxy, C_1-C_2 thioalkyl, C_2-C_3 thioalkenyl, C_2-C_3 thioalkynyl, $NR^{11}R^{12}$, aldehyde and ketone, wherein the alkyl, alkenyl, alkynyl, alkoxy, thioalkyl, thioalkenyl, and thioalkynyl groups are optionally substituted with one or more fluorines, and the acyl is optionally substituted with one or more halogens;	C_1-C_2 alkyl, C_2-C_3 alkenyl, C_2-C_3 alkynyl, C_1-C_2 alkoxy, C_1-C_2 thioalkyl, C_2-C_3 thioalkenyl, C_2-C_3 thioalkynyl, and $NR^{11}R^{12}$, wherein the alkyl, alkenyl, alkynyl, alkoxy, thioalkyl, thioalkenyl, and thioalkynyl groups are optionally substituted with one or more fluorines;	H, halogen, C_1-C_2 alkyl, C_2-C_3 alkenyl, C_2-C_3 alkynyl, and $NR^{10}R^{11}$, wherein the alkyl, alkenyl and alkynyl groups are optionally substituted with one or more fluorines;

	Markush Group A	Markush Group B	Markush Group C	Markush Group D
R^3	H, halogen, nitro, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, C_1-C_{10} alkoxy, C_1-C_{10} thioalkyl, C_2-C_{10} thioalkenyl, C_2-C_{10} thioalkynyl, $NR^{14}R^{15}$, and a carbocyclic or heterocyclic ring optionally substituted with up to two R_{19}, wherein the alkyl, alkenyl, alkynyl, alkoxy, thioalkyl, thioalkenyl, and thioalkynyl groups are optionally substituted with one or more halogens;	H, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_1-C_6 thioalkyl, C_2-C_6 thioalkenyl, C_2-C_6 thioalkynyl, $NR^{13}R^{14}$, and a carbocyclic ring optionally substituted with one or more fluorines or nitro groups, wherein the alkyl, alkenyl, alkynyl, alkoxy, thioalkyl, thioalkenyl and thioalkynyl groups are optionally substituted with one or more halogens;	H, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, and C_1-C_4 alkoxy group, wherein the alkyl, alkenyl, alkynyl and alkoxy groups are optionally substituted with one or more halogens;	C_1-C_2 alkyl and C_1-C_2 alkoxy wherein the alkyl and alkoxy groups are optionally substituted with one or more fluorines;
R^4	H, halogen, and OH	H and halogen	halogen	H
R^5	CH_2OH, CHO, and COOH, and $C(R'_5)(R''_5)(COOH)$	CH_2OH, CHO, and COOH	CH_2OH and COOH	$C(R'^5)(R''^5)(COOH)$
$R^{5'}$	H, O, S, and F; or $R^{5'}$ and $R^{5''}$ together form an O or S	H, O, and S or	H, O, and S; or $R^{5'}$ and $R^{5''}$ together form an S	
		$R^{5'}$ and $R^{5''}$ together form an O;		
$R^{5'}$	H, O, S, and F; or $R^{5'}$ and $R^{5''}$ together form an O or S	H, O, S and F; or		
		$R^{5'}$ and $R^{5''}$ together form an O or S;		

	Markush Group A	Markush Group B	Markush Group C	Markush Group D
R^6	H, halogen, C_1-C_{12} alkyl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, C_1-C_{12} alkoxy, C_1-C_{12} thioalkyl, C_2-C_{12} thioalkenyl, C_2-C_{12} thioalkynyl, $NR^{16}R^{17}$ and $NHC(O)R^{18}$, wherein the alkyl, alkenyl, alkynyl, alkoxy, thioalkyl, thioalkenyl and thioalkynyl groups are optionally substituted with one or more R^{19}; or	H, halogen, C_3-C_{12} alkyl, C_3-C_{12} alkenyl, C_3-C_{12} alkynyl, C_3-C_{12} alkoxy, C_3-C_{12} thioalkyl, C_3-C_{12} thioalkenyl, C_3-C_{12} thioalkynyl, $NR^{16}R^{17}$ and $NHC(O)R^{18}$, wherein the alkyl, alkenyl, alkynyl, alkoxy, thioalkyl, thioalkenyl and thioalkynyl groups are optionally substituted with up to two R^{19}	H, halogen, C_4-C_8 alkyl, C_4-C_8 alkenyl, C_4-C_8 alkynyl, C_4-C_8 alkoxy, C_4-C_8 thioalkyl, C_4-C_8 thioalkenyl, C_4-C_8 thioalkynyl, and NHR^{15}, wherein said alkyl, alkenyl, alkynyl, alkoxy, thioalkyl, thioalkenyl and thioalkynyl groups are optionally substituted with one or more R^{10}; or	H, Cl, Br and F H and halogen
	R^5 and R^7 taken together form an O, S, NH or CH_2		R_6 and R_7 taken together are O, S or NH;	

	Markush Group A	Markush Group B	Markush Group C	Markush Group D
R^7	H, halogen, C_1-C_{12} alkyl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, C_1-C_{12} alkoxy, C_1-C_{12} thioalkyl, C_2-C_{12} thioalkenyl, C_2-C_{12} thioalkynyl, $NR^{16}R^{17}$ and $NHC(O)R^{18}$, wherein the alkyl, alkenyl, alkynyl, alkoxy, thioalkyl, thioalkenyl and thioalkynyl groups are optionally substituted with one or more R^{19}; or	H, halogen, C_1-C_{12} alkyl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, C_1-C_{12} alkoxy, C_1-C_{12} thioalkyl, C_2-C_{12} thioalkenyl, C_2-C_{12} thioalkynyl, $NR^{16}R_{17}$ and $NHC(O)R^{18}$, wherein the alkyl, alkenyl, alkynyl, alkoxy, thioalkyl, thioalkenyl and thioalkynyl groups are optionally substituted with up to two R^{19}	H, halogen, C_4-C_{12} alkyl, C_4-C_{12} alkenyl, C_4-C_{12} alkynyl, C_3-C_{12} alkoxy, C_3-C_{12} thioalkyl, C_3-C_{12} thioalkenyl, C_3-C_{12} thioalkynyl, and NHR^{15}, wherein said alkyl, alkenyl, alkynyl, alkoxy, thioalkyl, thioalkenyl and thioalkynyl groups are optionally substituted with one or more R^{10}; or	H and F
	R^6 and R^7 taken together form an O, S, NH or CH_2		R_6 and R_7 taken together are oxygen, sulfur or nitrogen;	
R^8	H, halogen, methyl optionally substituted with one or more halogens and null; or	H and methyl optionally substituted with one or more halogens;	null	
	R^8 and R^9 taken together with Y form a three to five-membered carbocyclic ring;			

	Markush Group A	Markush Group B	Markush Group C	Markush Group D
R^9	H, halogen, methyl optionally substituted with one or more halogens and null; or	H and methyl optionally substituted with one or more halogens;	null	methyl op. sub
	R^8 and R^9 taken together with Y form a three to five-membered carbocyclic ring;			
R^{10}	H, halogen, methyl optionally substituted with one or more fluorines, and thiomethyl optionally substituted with one or more halogens;	H, halogen, and methyl optionally substituted with one or more halogens;	C_1-C_3 alkyl optionally substituted with one or more halogens;	methyl op. sub
R^{11}	H, halogen and OH; or	OH	C_1-C_3 alkyl optionally substituted with one or more halogens; or	Halogen
	R^{11} and $R^{11'}$ taken together form an oxygen;		R^{11} and R^{12} taken together with the nitrogen to which they are both bound form a five to six-membered heterocyclic ring;	
$R^{11'}$	H, halogen and OH; or	H	halogen and OH	Halogen
	R^{11} and $R^{11'}$ taken together form an oxygen;			

	Markush Group A	Markush Group B	Markush Group C	Markush Group D
R^{12}	C_1-C_6 alkyl optionally substituted with one or more halogens; or	C_1-C_3 alkyl optionally substituted with one or more halogens; or	C_4-C_5 alkyl optionally substituted with one or more halogens, phenyl optionally substituted with one or more fluorines, thienyl optionally substituted with one or more fluorines, and benzyl optionally substituted with one or more R^{13};	methyl op. sub
	R^{12} and R^{13} taken together with the nitrogen atom to which they are both bound to form a five to six-membered heterocyclic ring	R^{11} and R^{12} taken together with the nitrogen to which they are both bound form a five to six-membered heterocyclic ring;		

	Markush Group A	Markush Group B	Markush Group C	Markush Group D
R^{13}	C_1-C_3 alkyl optionally substituted with one or more halogens; or	C_1-C_2 alkyl optionally substituted with one or more halogens;	halogen, methyl optionally substituted with one or more fluorines, and thiomethyl optionally substituted with one or more halogens;	methyl
	R^{12} and R^{13} taken together with the nitrogen atom to which they are both bound to form a five to six-membered heterocyclic ring			
R^{14}	C_1-C_2 alkyl optionally substituted with one or more halogens;	C_1-C_2 alkyl optionally substituted with one or more halogens;	Methyl op. sub.	
R^{15}	C_1-C_2 alkyl optionally substituted with one or more halogens;	benzyl optionally substituted with one or more fluorines;	Methyl op. sub.	
R^{16}	C_1-C_{12} alkyl, C_2-C_{12} alkenyl, C_1-C_{12} alkynyl, a carbocyclic ring, and a heterocyclic ring, wherein the alkyl, alkenyl, alkynyl, carbocyclic ring and heterocyclic ring groups are optionally substituted with one or more R^{19}; or	C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, a carbocyclic ring and a heterocyclic ring, wherein the alkyl, alkenyl, alkynyl, carbocyclic ring and heterocyclic ring groups are optionally substituted with one or more R^{19};	C_2-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, a carbocyclic ring and a heterocyclic ring, wherein the alkyl, alkenyl, alkynyl, carbocyclic ring and heterocyclic ring groups are optionally substituted with one or more R^{19};	C_2-C_4 alkyl optionally substituted with one or more R^{19}
	R^{16} and R^{17} taken together with the nitrogen atom to			

	Markush Group A	Markush Group B	Markush Group C	Markush Group D
	which they are both bound form a five to six-membered heterocyclic ring;			
R^{17}	C_1-C_{12} alkyl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, a carbocyclic ring, and a heterocyclic ring, wherein the alkyl, alkenyl, alkynyl, carbocyclic ring and heterocyclic ring groups are optionally substituted with one or more R_{19}; or			
	R^{16} and R^{17} taken together with the nitrogen atom to which they are both bound form a five to six-membered heterocyclic ring;			
R^{18}	C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynyl, a carbocyclic ring, and a heterocyclic ring, wherein the alkyl, alkenyl and alkynyl groups are optionally substituted with one or more halogens, and the carbocyclic ring and heterocyclic ring groups are optionally substituted with one or more R_{19};	C_2-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, a carbocyclic ring, and a heterocyclic ring, wherein the alkyl, alkenyl and alkynyl groups are optionally substituted with one or more halogens, and the carbocyclic ring and heterocyclic ring groups are optionally substituted with one or more R_{19};	C_2-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, a carbocyclic ring and a heterocyclic ring, wherein the alkyl, alkenyl and alkynyl groups are optionally substituted with one or more halogens, and the carbocyclic ring and heterocyclic ring groups are optionally substituted with one or more R_{19};	

	Markush Group A	Markush Group B	Markush Group C	Markush Group D
R^{19}	halogen, C_1-C_4 alkyl optionally substituted with one or more halogens, C_1-C_4 alkoxy optionally substituted with one or more halogens, C_1-C_3 thioalkyl group optionally substituted with one or more halogens, formyl and nitro;	C_1-C_4 alkyl optionally substituted with one or more fluorines, C_1-C_4 alkoxy optionally substituted with one or more halogens, C_1-C_3 thioalkyl group optionally substituted with one or more halogens	C_1-C_2 alkyl optionally substituted with one or more fluorines	
A	O, CH_2, CF_2 and S	O, CH_2 and S	O, CF_2 and S	O and S
X	carbon, oxygen, nitrogen and sulfur	carbon, oxygen and sulfur;	oxygen and nitrogen	
Y	carbon, oxygen, sulfur and nitrogen	nitrogen	oxygen and sulfur	
Z	carbon, nitrogen and phenyl			

[0140] In certain embodiments, the invention provides compounds selected from: 4-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethoxy-2-naphthalenyl]benzoyl benzoic acid (Compound 103);

4-[5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-1-hydroxy-2-naphthalenyl]benzoyl benzoic acid (Compound 104);

4-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-(1,1,1-trifluoroethoxy)-2-naphthalenyl]benzoyl benzoic acid (Compound 105);

4-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-propoxy-2-naphthalenyl]benzoyl benzoic acid (Compound 106);

4-[5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-4-nitro-2-naphthalenyl]benzoyl benzoic acid (Compound 108);

4-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethoxy-4-nitro-2-naphthalenyl]benzoyl benzoic acid (Compound 109);

4-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-(2,2-difluoroethoxy)-4-nitro-2-naphthalenyl]benzoyl benzoic acid (Compound 110);

4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-methoxy-2-naphthalenyl)methyl]benzoic acid (Compound 117);

4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-*iso*-propoxy-2-naphthalenyl)methyl]benzoic acid (Compound 118);

4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethoxy-2-naphthalenyl)methyl]benzoic acid (Compound 119);

4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-(1,1,1-trifuoroethoxy)-2-naphthalenyl)methyl]benzoic acid (Compound 120);

4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-propoxy-2-naphthalenyl)methyl]benzoic acid (Compound 121);

4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-butoxy-2-naphthalenyl)methyl]benzoic acid (Compound 122);

4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-heptoxy-2-naphthalenyl)methyl]benzoic acid (Compound 123);

4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-methyl-4-*p*-tolenesulfonamido-2-naphthalenyl) methyl]benzoic acid (Compound 124);

4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-methyl-4-ethylamino-2-naphthalenyl)methyl]benzoic acid (Compound 125);

4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-methyl-4-propylamino-2-naphthalenyl)methyl] benzoic acid (Compound 126);

4-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-(2-fluorophenyl)-2-naphthalenyl]benzoyl benzoic acid (Compound 128);

4-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-phenyl-2-naphthalenyl]benzoyl benzoic acid (Compound 129);

4-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-(3-thienyl)-2-naphthalenyl]benzoyl benzoic acid (Compound 130);

4-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-(4-fluorophenyl)-2-naphthalenyl]benzoyl benzoic acid (Compound 131);

4-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-(3-nitrophenyl)-2-naphthalenyl]benzoyl benzoic acid (Compound 132);

4-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-(*N*-methyl-*N*-ethylamino)-2-naphthalenyl]benzoyl benzoic acid (Compound 134);

4-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-(2-fluorophenyl)-4-nitro-2-naphthalenyl]benzoyl benzoic acid (Compound 136);

4-[(5,6,7,8-tetrahydro-3,8,8-trimethyl-4-nitro-2-naphthalenyl)benzoyl] benzoic acid (Compound 137);

4-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-1-fluoro-3-ethoxy-2-naphthalenyl]benzoyl benzoic acid (Compound 141);

4-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-1-fluoro-3-ethoxy-4-nitro-2-naphthalenyl] benzoyl benzoic acid (Compound 142);

4-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethoxy-2-naphthalenyl]benzoyl-3-chloro-benzoic acid (Compound 144);

4-[(5,6,7,8-tetrahydro-3,5,5,8,8-tetramethyl-2-naphthalenyl)(2-fluorobenzyloxy) methyl] benzoic acid (Compound 149);

4-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)(4-fluorobenzyloxy) methyl]benzoic acid (Compound 150);

4-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)(2-thifluoromethoxy benzyloxy) methyl]benzoic acid (Compound 151);

4-[(5,6,7,8-tetrahydro-3,5,5,8,8-tetramethyl-2-naphthalenyl)(2,3-difluorobenzyloxy) methyl] benzoic acid (Compound 152);

4-[(5,6,7,8-tetrahydro-3,5,5,8,8-tetramethyl-2-naphthalenyl)(4-trifluoromethyl benzyloxy) methyl] benzoic acid (Compound 153);

4-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)(4-trifluoromethoxy benzyloxy) methyl] benzoic acid (Compound 154);

4-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)(4-trifluorothiomethoxy benzyloxy) methyl] benzoic acid (Compound 155);

4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethoxy-2-naphthalenyl)(2,3-difluoro benzyloxy) methyl]benzoic acid (Compound 156);

4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethoxy-2-naphthalenyl)(4-fluoro benzyloxy)methyl] benzoic acid (Compound 157);

4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethoxy-2-naphthalenyl)(2-fluorobenzyloxy)methyl] benzoic acid (Compound 158);

4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethoxy-2-naphthalenyl) (benzyloxy)methyl]benzoic acid (Compound 159);

4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethoxy-2-naphthalenyl) (butyloxy)methyl]benzoic acid (Compound 160);

4-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)(phenylacetamido) methyl] benzoic acid (Compound 162);

4-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)(3-fluorobenzylamino) methyl] benzoic acid (Compound 163);

4-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)(4-fluorobenzylamino) methyl] benzoic acid (Compound 164);

4-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)(benzylamino) methyl] benzoic acid (Compound 165);

4-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)(4-trifluoromethyl phenoxy)methyl]benzoic acid (Compound 166);

4-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)(4-*tert*-butylbenzylthio)methyl] benzoic acid (Compound 167);

4-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)(4-fluorophenyloxy)methyl]benzoic acid (Compound 168);

4-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)(4-*tert*-butylphenyloxy) methyl]benzoic acid (Compound 169);

4-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)(4-phenylphenyloxy) methyl]benzoic acid (Compound 170);

4-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)(4-phenoxy) methyl]benzoic acid (Compound 171);

4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethoxy-2-naphthalenyl)(4-*tert*-butylbenzylthio) methyl]benzoic acid (Compound 172);

4-[(phenylhydrazino)(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)]benzoic acid (Compound 173);

4-[(phenylhydrazino)(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)] benzoic acid (Compound 174);

4-[(phenylhydrazino)(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-4-ethoxy-2-naphthalenyl)]benzoic acid (Compound 175);

4-[(Pyridine-2-hydrazonyl)(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethyloxy-2-naphthalenyl)]benzoyl benzoic acid (Compound 176);

4-[(2,4-difluorophenylhydrazino)(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-4-ethoxy-2-naphthalenyl)]benzoic acid (Compound 177);

4-[(2,5-difluorophenylhydrazino)(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-4-ethoxy-2-naphthalenyl)]benzoic acid (Compound 178);

4-[(2,5-dimethylphenylhydrazino)(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-4-ethoxy-2-naphthalenyl)]benzoic acid (Compound 179);

4-[(2-fluorophenylhydrazino)(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)]benzoic acid (Compound 180);

4-[(phenylimino)(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-4-ethoxy-2-naphthalenyl)] benzoic acid (Compound 183);

4-[(4,4,4-trifluorobutoximino)(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethyloxy-2-naphthalenyl)]benzoic acid (Compound 184);

4-[(ethoxyimino)(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethyloxy-2-naphthalenyl)] benzoic acid (Compound 185);

4-[(propoxyimino)(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethyloxy -2-naphthalenyl)]benzoic acid (Compound 186);

4-[(butoxyimino)(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethyloxy-2-naphthalenyl)]benzoic acid (Compound 187);

4-[(pentoxyimino)(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethyloxy-2-naphthalenyl)]benzoic acid (Compound 188);

4-[(hexyloxyimino)(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethyloxy-2-naphthalenyl)]benzoic acid (Compound 189);

4-[(3-methyl-butoxyimino)(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethyloxy-2-naphthalenyl)] benzoic acid (Compound 190);

4-[(decyloxyimino)(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethyloxy-2-naphthalenyl)]benzoic acid (Compound 191);

4-[(2,3-difluorobenzyloxyimino)(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethyloxy-2-naphthalenyl)] benzoic acid (Compound 192);

6-(2,3-dihydro-4,4-dimethyl-7-ethoxybenzopyranyl)benzoyl benzoic acid (Compound 201);

6-[(2,3-dihydro-4,4-dimethyl-7-ethoxy-benzothiopyranyl)]benzoyl benzoic acid (Compound 202);

6-(2,3-dihydro-4,4,7-trimethyl-8nitro-benzopyranyl)benzoyl benzoic acid (Compound 203);

7-[1,4,4-trimethyl-5-methyl-6-methoxy1,2,3,4-tetrahydroquinoline]benzoyl benzoic acid (Compound 212);

7-[1,4,4-trimethyl-5-methyl-6-ethoxy1,2,3,4-tetrahydroquinoline]benzoyl benzoic acid (Compound 213);

4-[(5,6,7,8-tetrahydro-3,8,8-trimethyl-2-naphthalenyl)ethenyl] benzoic acid (Compound 214);

2-Oxo-2-[4-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethyloxy-2-naphthalenyl]phenyl]acetic acid (compound 217); and

2-Oxo-2-[4-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-methyl-2-naphthalenyl]phenyl]acetic acid (compound 218);

and pharmaceutically acceptable salts, esters, amides, and/or prodrugs of any of those compounds.

[0141] In certain embodiments, a compound of Formula I, II, III, IV, V, or VI is a selective HNF-4α receptor modulator. In certain embodiments, a compound of Formula I, II, III, IV, V, or VI is a selective HNF-4α receptor agonist. In certain embodiments, a compound of Formula I, II, III, IV, V, or VI is a selective HNF-4α receptor antagonist. In certain embodiments, a compound of Formula I, II, III, IV, V, or VI is a selective HNF-4α receptor partial agonist. In certain embodiments, a compound of Formula I, II, III, IV, V, or VI is a tissue-specific selective HNF-4α receptor modulator. In certain embodiments, a compound of Formula I, II, III, IV, V, or VI is a gene-specific selective HNF-4α receptor modulator. In certain embodiments, a compound of Formula I, II, III, IV, V, or VI is a selective HNF-4α receptor binding compound.

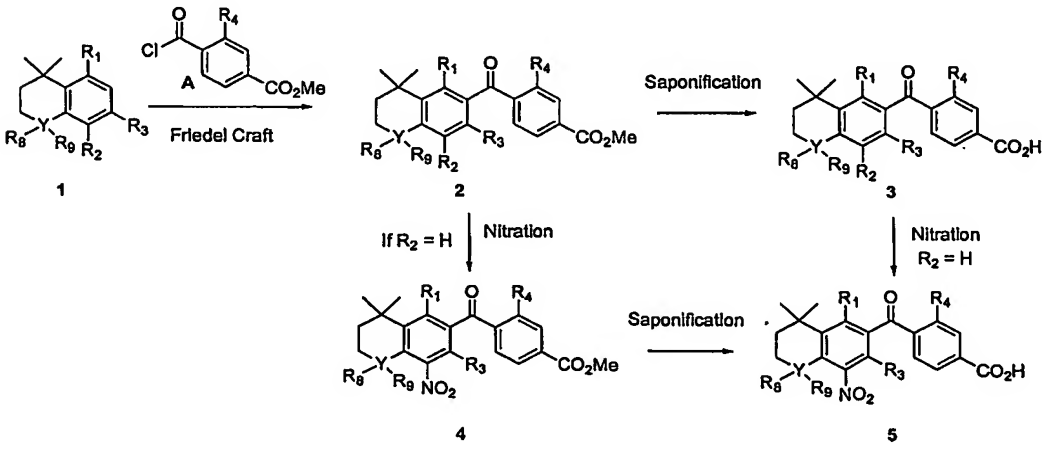
[0142] In certain embodiments, the present invention provides selective HNF-4α receptor modulators. In certain embodiments, the invention provides selective HNF-4α receptor binding agents. In certain embodiments, the invention provides methods of

making and methods of using selective HNF-4α receptor modulators and/or selective HNF-4α binding agents. In certain embodiments, selective HNF-4α modulators are agonists, partial agonists, and/or antagonists for the HNF-4α receptor. In certain embodiments, the invention provides compounds that are selective for an HNF-4α receptor relative to a retinoic X receptor (RXR) (*e.g.*, Compounds 104, 105, 110, 124, 125, 126, 158, 163, 171, 173, 177, 179, 190, 192, 201, 202, 212, 213, 214, 215, 217, and 218). In certain embodiments, the invention provides compounds that are selective for an HNF-4α receptor relative to an RXR by at least 8 times.

Certain Synthesis Methods

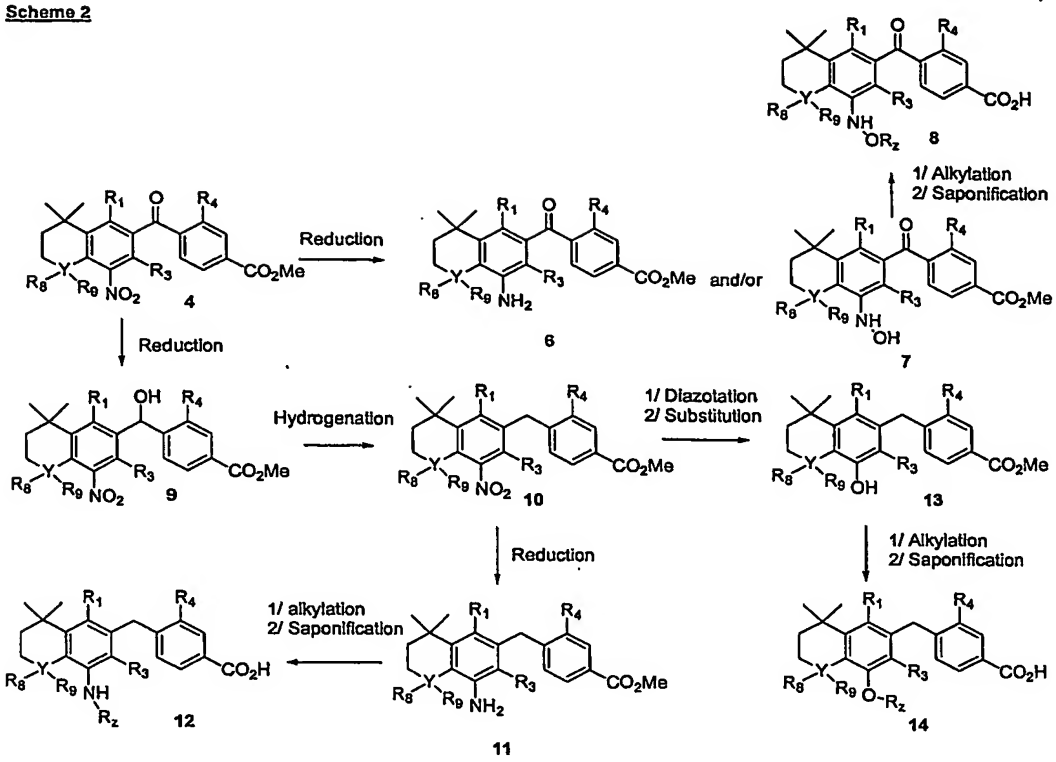
[0143] Certain synthesis schemes are now provided. The synthesis schemes are provide only to illustrate possible ways to make certain compounds of the invention and do not limit the invention in any way. One of skill in the art will recognize that compounds of the present invention may be synthesized through any of a variety of schemes using a variety of different starting materials.

Scheme 1



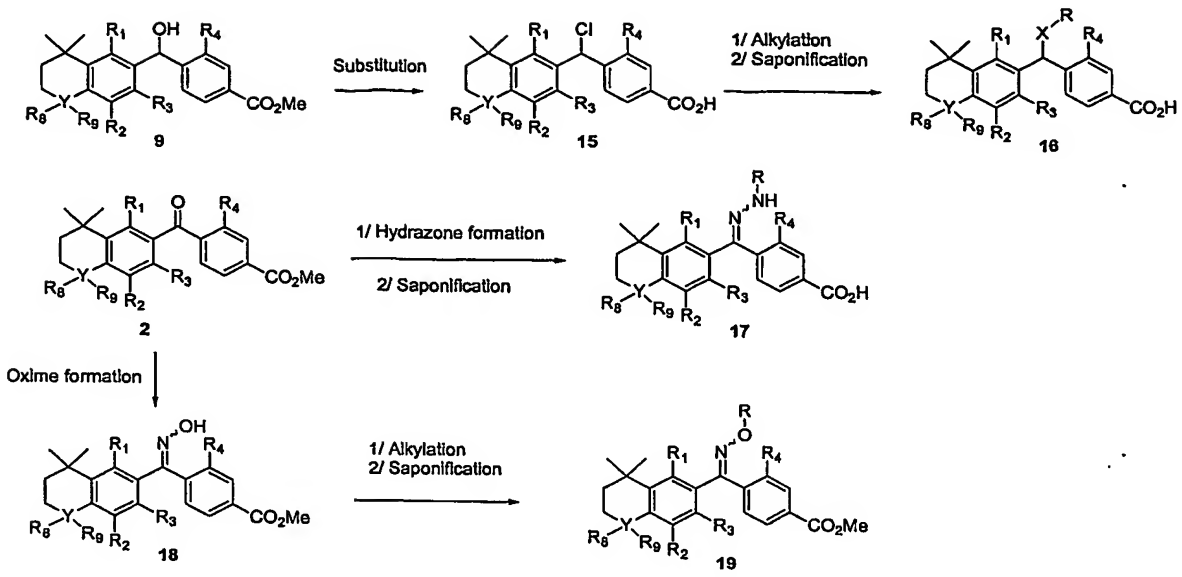
The intermediate **2** are usually obtained by a Friedel-Craft reaction between **1** and **A** in the presence of $AlCl_3$ in CH_2Cl_2. Saponification of **2** affords the acids **3**. In the case of R_2 = H, **2** can be nitrated using a mixture of HNO_3/H_2SO_4 in acetic acid at room temperature to give **4**. The derivatives **5** may be obtained by saponification of **4** or by selective nitration of **3** (R_2 = H in **3**). The nitro group present in **4** can be reduced to the corresponding amine **6** or hydroxylamine **7** using Zinc dust in $MeOH/H_2O/CH_2Cl_2$ at room temperature. **7** can be O-alkylated with various alkyl iodide or bromide ($X\text{-}R_z$) in the presence of K_2CO_3 in DMF at room temperature. Reduction with $NaBH_4$ of the benzophenone **4** affords the alcohol **9**. Removal of the hydroxyl by catalytic hydrogenation (H_2/Pd/C) yields the methylene-bridged derivatives **10**. Reduction of the nitro group on **10** releases the amino derivatives **11**. The amino group of **11** may be alkylated and saponificated to afford the acids **12**. Diazotation followed by nucleophilic displacement of **10** affords the phenols **13**. These are then alkylated and saponified to give the derivatives **14**.

Scheme 2



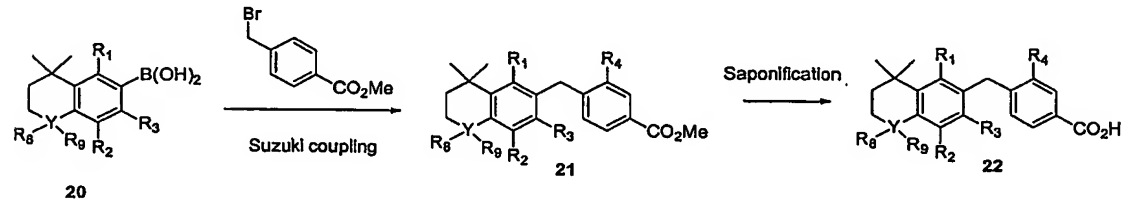
Derivatives **9** could be transformed into the chlorines **15** that can be used as alkylating agents with alcohols, amines or thiols. Saponification of these adducts afford the acids **16**. The hydrazones **17** and the oximes **18** and **19** are easily synthesized from the ketones **2**.

Scheme 3



Alternatively, the following scheme using a Suzuki coupling between the boronic acids **20** and methyl 4-bromomethyl benzoate followed by saponification may be used to synthesize the derivatives **22**.

Scheme 4



[0144] In certain embodiments, the invention provides a salt corresponding to any of the compounds provided herein. In certain embodiments, the invention provides a

salt corresponding to a selective HNF-4α modulator. In certain embodiments, the invention provides a salt corresponding to a selective HNF-4α receptor binding agent. In certain embodiments, a salt is obtained by reacting a compound with an inorganic acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like. In certain embodiments, a salt is obtained by reacting a compound with a base to form a salt such as an ammonium salt, an alkali metal salt, such as a sodium or a potassium salt, an alkaline earth metal salt, such as a calcium or a magnesium salt, a salt of organic bases such as dicyclohexylamine, N-methyl-D-glucamine, tris(hydroxymethyl)methylamine, and salts with amino acids such as arginine, lysine, and the like.

[0145] In certain embodiments, one or more carbon atoms of a compound of the present invention is replaced with silicon. *See e.g.*, WO 03/037905A1; Tacke & Zilch, *Endeavour, New Series*, 10:191-197 (1986); Bains & Tacke, *Curr. Opin. Drug Discov Devel.* 6:526-43 (2003). In certain embodiments, compounds of the present invention comprising one or more silicon atoms possess certain desired properties, including, but not limited to, greater stability and/or longer half-life in a patient, when compared to the same compound in which none of the carbon atoms have been replaced with a silicon atom.

[0146] Protecting groups that may be used in the present invention include those that are commonly known to those skilled in the art, such groups include, but are not limited to TBDMS, TBS and Benzyl.

Certain Assays

[0147] In certain embodiments, compounds of the present invention are capable of modulating activity of HNF-4α receptors in a "co-transfection" assay (also called a "cis-trans" assay), which has been discussed previously. *See e.g.*, Evans *et al.*, *Science*, 240:889-95 (1988); U.S. Patent Nos. 4,981,784 and 5,071,773; Pathirana *et al.*, *Mol. Pharm.* 47:630-35 (1995)). Modulating activity in a co-transfection assay has been shown to correlate with *in vivo* modulating activity. Thus, in certain embodiments, such assays are predictive of *in vivo* activity. *See, e.g.*, Berger *et al.*, *J. Steroid Biochem. Molec. Biol.* 41:773 (1992).

[0148] In certain co-transfection assays, two different co-transfection plasmids are prepared. In the first co-transfection plasmid, cloned cDNA encoding an intracellular receptor (*e.g.*, HNF-4α receptor) is operatively linked to a constitutive promoter (*e.g.*, the SV40 promoter). In the second co-transfection plasmid, cDNA encoding a reporter protein, such as firefly luciferase (LUC), is operatively linked to a promoter that is activated by a receptor-dependant activation factor. Both co-transfection plasmids are co-transfected into the same cells. Expression of the first co-transfection plasmid results in production of the intracellular receptor protein. Activation of that intracellular receptor protein (*e.g.*, by binding of an agonist) results in production of a receptor-dependant activation factor for the promoter of the second co-transfection plasmid. That receptor-dependant activation factor in turn results in expression of the reporter protein encoded on the second co-transfection plasmid. Thus, reporter protein expression is linked to activation of the receptor. Typically, that reporter activity can be conveniently measured (*e.g.*, as increased luciferase production).

[0149] Certain co-transfection assays can be used to identify agonists, partial agonists, and/or antagonists of intracellular receptors. In certain embodiments, to identify agonists, co-transfected cells are exposed to a test compound. If the test compound is an agonist or partial agonist, reporter activity is expected to be higher compared to co-transfected cells in the absence of the test compound. In certain embodiments, to identify antagonists, the cells are exposed to a known agonist (*e.g.*, the natural ligand for the receptor) in the presence and absence of a test compound. If the test compound is an antagonist, reporter activity is expected to be lower than that of cells exposed only to the known agonist.

[0150] In certain embodiments, compounds of the invention are used to detect the presence, quantity and/or state of receptors in a sample. In certain of such embodiments, samples are obtained from a patient. In certain embodiments, compounds are radio- or isotopically-labeled. For example, compounds of the present invention that selectively bind HNF-4α receptors may be used to determine the presence or amount of such receptors in a sample, such as cell homogenates and lysates.

[0151] In certain embodiments, the present invention provides for use of both CARLA and mammalian-2-hybrid assays, to characterize the *in vitro* profile of compounds of the invention on a HNF-4α receptor.

[0152] In certain embodiments, the present invention provides for use of $[H]^3$-[4-[(phenylhydrazino)(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)]benzoic acid] (Example 73) and/or $[H]^3$-4-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethoxy-2-naphthalenyl]benzoyl benzoic acid (Example 3) as radioactive ligands for a binding assay.

Certain Pharmaceutical Agents

[0153] In certain embodiments, at least one selective HNF-4α receptor modulator, or pharmaceutically acceptable salt, ester, amide, and/or prodrug thereof, either alone or combined with one or more pharmaceutically acceptable carriers, forms a pharmaceutical agent. Techniques for formulation and administration of compounds of the present invention may be found for example, in "Remington's Pharmaceutical Sciences," Mack Publishing Co., Easton, PA, 18th edition, 1990.

[0154] In certain embodiments, a pharmaceutical agent comprising one or more compounds of the present invention is prepared using known techniques, including, but not limited to mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or tabletting processes.

[0155] In certain embodiments, a pharmaceutical agent comprising one or more compounds of the present invention is a liquid (*e.g.*, a suspension, elixir and/or solution). In certain of such embodiments, a liquid pharmaceutical agent comprising one or more compounds of the present invention is prepared using ingredients known in the art, including, but not limited to, water, glycols, oils, alcohols, flavoring agents, preservatives, and coloring agents.

[0156] In certain embodiments, a pharmaceutical agent comprising one or more compounds of the present invention is a solid (*e.g.*, a powder, tablet, and/or capsule). In certain of such embodiments, a solid pharmaceutical agent comprising one or more compounds of the present invention is prepared using ingredients known in the art, including, but not limited to, starches, sugars, diluents, granulating agents, lubricants, binders, and disintegrating agents.

[0157] In certain embodiments, a pharmaceutical agent comprising one or more compounds of the present invention is formulated as a depot preparation. Certain of such depot preparations are typically longer acting than non-depot preparations. In certain embodiments, such preparations are administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. In certain embodiments, depot preparations are prepared using suitable polymeric or hydrophobic materials (for example an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

[0158] In certain embodiments, a pharmaceutical agent comprising one or more compounds of the present invention comprises a delivery system. Examples of delivery systems include, but are not limited to, liposomes and emulsions. Certain delivery systems are useful for preparing certain pharmaceutical agents including those comprising hydrophobic compounds. In certain embodiments, certain organic solvents such as dimethylsulfoxide are used.

[0159] In certain embodiments, a pharmaceutical agent comprising one or more compounds of the present invention comprises one or more tissue-specific delivery molecules designed to deliver the pharmaceutical agent to specific tissues or cell types. For example, in certain embodiments, pharmaceutical agents include liposomes coated with a tissue-specific antibody.

[0160] In certain embodiments, a pharmaceutical agent comprising one or more compounds of the present invention comprises a co-solvent system. Certain of such co-solvent systems comprise, for example, benzyl alcohol, a nonpolar surfactant, a water-miscible organic polymer, and an aqueous phase. In certain embodiments, such co-solvent systems are used for hydrophobic compounds. A non-limiting example of such a

co-solvent system is the VPD co-solvent system, which is a solution of absolute ethanol comprising 3% w/v benzyl alcohol, 8% w/v of the nonpolar surfactant Polysorbate 80™, and 65% w/v polyethylene glycol 300. The proportions of such co-solvent systems may be varied considerably without significantly altering their solubility and toxicity characteristics. Furthermore, the identity of co-solvent components may be varied: for example, other surfactants may be used instead of Polysorbate 80™; the fraction size of polyethylene glycol may be varied; other biocompatible polymers may replace polyethylene glycol, *e.g.*, polyvinyl pyrrolidone; and other sugars or polysaccharides may substitute for dextrose.

[0161] In certain embodiments, a pharmaceutical agent comprising one or more compounds of the present invention comprises a sustained-release system. A non-limiting example of such a sustained-release system is a semi-permeable matrix of solid hydrophobic polymers. In certain embodiments, sustained-release systems may, depending on their chemical nature, release compounds over a period of hours, days, weeks or months.

[0162] Certain compounds used in pharmaceutical agent of the present invention may be provided as pharmaceutically acceptable salts with pharmaceutically compatible counterions. Pharmaceutically compatible salts may be formed with many acids, including but not limited to hydrochloric, sulfuric, acetic, lactic, tartaric, malic, succinic, etc.

[0163] In certain embodiments, a pharmaceutical agent comprising one or more compounds of the present invention comprises an active ingredient in a therapeutically effective amount. In certain embodiments, the therapeutically effective amount is sufficient to prevent, alleviate or ameliorate symptoms of a disease or to prolong the

survival of the subject being treated. Determination of a therapeutically effective amount is well within the capability of those skilled in the art.

[0164] In certain embodiments, a pharmaceutical agent comprising one or more compounds of the present invention is formulated as a prodrug. In certain embodiments, prodrugs are useful because they are easier to administer than the corresponding active form. For example, in certain instances, a prodrug may be more bioavailable (*e.g.*, through oral administration) than is the corresponding active form. In certain instances, a prodrug may have improved solubility compared to the corresponding active form. In certain embodiments, a prodrug is an ester. In certain embodiments, such prodrugs are less water soluble than the corresponding active form. In certain instances, such prodrugs possess superior transmittal across cell membranes, where water solubility is detrimental to mobility. In certain embodiments, the ester in such prodrugs is metabolically hydrolyzed to carboxylic acid. In certain instances the carboxylic acid containing compound is the corresponding active form. In certain embodiments, a prodrug comprises a short peptide (polyaminoacid) bound to an acid group. In certain of such embodiments, the peptide is metabolized to form the corresponding active form.

[0165] In certain embodiments, a pharmaceutical agent comprising one or more compounds of the present invention is useful for treating a conditions or disorder in a mammalian, and particularly in a human patient. Suitable administration routes include, but are not limited to, oral, rectal, transmucosal, intestinal, enteral, topical, suppository, through inhalation, intrathecal, intraventricular, intraperitoneal, intranasal, intraocular and parenteral (*e.g.*, intravenous, intramuscular, intramedullary, and subcutaneous). In certain embodiments, pharmaceutical intrathecals are administered to achieve local rather

than systemic exposures. For example, pharmaceutical agents may be injected directly in the area of desired effect (*e.g.*, in the renal or cardiac area).

[0166] In certain embodiments, a pharmaceutical agent comprising one or more compounds of the present invention is administered in the form of a dosage unit (*e.g.*, tablet, capsule, bolus, etc.). In certain embodiments, such dosage units comprise a selective a HNF-4α receptor modulator in a dose from about 1 μg/kg of body weight to about 50 mg/kg of body weight. In certain embodiments, such dosage units comprise a selective a HNF-4α receptor modulator in a dose from about 2 μg/kg of body weight to about 25 mg/kg of body weight. In certain embodiments, such dosage units comprise a selective a HNF-4α receptor modulator in a dose from about 10 μg/kg of body weight to about 5 mg/kg of body weight. In certain embodiments, pharmaceutical agents are administered as needed, once per day, twice per day, three times per day, or four or more times per day. It is recognized by those skilled in the art that the particular dose, frequency, and duration of administration depends on a number of factors, including, without limitation, the biological activity desired, the condition of the patient, and tolerance for the pharmaceutical agent.

[0167] In certain embodiments, a pharmaceutical agent comprising a compound of the present invention is prepared for oral administration. In certain of such embodiments, a pharmaceutical agent is formulated by combining one or more compounds of the present invention with one or more pharmaceutically acceptable carriers. Certain of such carriers enable compounds of the invention to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient. In certain embodiments, pharmaceutical agents for oral use are obtained by mixing one or more compounds of the present invention and one or

more solid excipient. Suitable excipients include, but are not limited to, fillers, such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP). In certain embodiments, such a mixture is optionally ground and auxiliaries are optionally added. In certain embodiments, pharmaceutical agents are formed to obtain tablets or dragee cores. In certain embodiments, disintegrating agents (*e.g.*, cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof, such as sodium alginate) are added.

[0168] In certain embodiments, dragee cores are provided with coatings. In certain of such embodiments, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to tablets or dragee coatings.

[0169] In certain embodiments, pharmaceutical agents for oral administration are push-fit capsules made of gelatin. Certain of such push-fit capsules comprise one or more compounds of the present invention in admixture with one or more filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In certain embodiments, pharmaceutical agents for oral administration are soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. In certain soft capsules, one or more compounds of the present invention are be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added.

[0170] In certain embodiments, pharmaceutical agents are prepared for buccal administration. Certain of such pharmaceutical agents are tablets or lozenges formulated in conventional manner.

[0171] In certain embodiments, a pharmaceutical agent is prepared for administration by injection (*e.g.*, intravenous, subcutaneous, intramuscular, etc.). In certain of such embodiments, a pharmaceutical agent comprises a carrier and is formulated in aqueous solution, such as water or physiologically compatible buffers such as Hanks's solution, Ringer's solution, or physiological saline buffer. In certain embodiments, other ingredients are included (*e.g.*, ingredients that aid in solubility or serve as preservatives). In certain embodiments, injectable suspensions are prepared using appropriate liquid carriers, suspending agents and the like. Certain pharmaceutical agents for injection are presented in unit dosage form, *e.g.*, in ampoules or in multi-dose containers. Certain pharmaceutical agents for injection are suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Certain solvents suitable for use in pharmaceutical agents for injection include, but are not limited to, lipophilic solvents and fatty oils, such as sesame oil, synthetic fatty acid esters, such as ethyl oleate or triglycerides, and liposomes. Aqueous injection suspensions may contain substances that increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, such suspensions may also contain suitable stabilizers or agents that increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

[0172] In certain embodiments, a pharmaceutical agent is prepared for transmucosal administration. In certain of such embodiments penetrants appropriate to

the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

[0173] In certain embodiments, a pharmaceutical agent is prepared for administration by inhalation. Certain of such pharmaceutical agents for inhalation are prepared in the form of an aerosol spray in a pressurized pack or a nebulizer. Certain of such pharmaceutical agents comprise a propellant, *e.g.*, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In certain embodiments using a pressurized aerosol, the dosage unit may be determined with a valve that delivers a metered amount. In certain embodiments, capsules and cartridges for use in an inhaler or insufflator may be formulated. Certain of such formulations comprise a powder mixture of a compound of the invention and a suitable powder base such as lactose or starch.

[0174] In certain embodiments, a pharmaceutical agent is prepared for rectal administration, such as a suppositories or retention enema. Certain of such pharmaceutical agents comprise known ingredients, such as cocoa butter and/or other glycerides.

[0175] In certain embodiments, a pharmaceutical agent is prepared for topical administration. Certain of such pharmaceutical agents comprise bland moisturizing bases, such as ointments or creams. Exemplary suitable ointment bases include, but are not limited to, petrolatum, petrolatum plus volatile silicones, lanolin and water in oil emulsions such as Eucerin™, available from Beiersdorf (Cincinnati, Ohio). Exemplary suitable cream bases include, but are not limited to, Nivea™ Cream, available from Beiersdorf (Cincinnati, Ohio), cold cream (USP), Purpose Cream™, available from

Johnson & Johnson (New Brunswick, New Jersey), hydrophilic ointment (USP) and Lubriderm™, available from Pfizer (Morris Plains, New Jersey).

[0176] In certain embodiments, the formulation, route of administration and dosage for a pharmaceutical agent of the present invention can be chosen in view of a particular patient's condition. (See *e.g.*, Fingl *et al.* 1975, in "The Pharmacological Basis of Therapeutics", Ch. 1 p. 1). In certain embodiments, a pharmaceutical agent is administered as a single dose. In certain embodiments, a pharmaceutical agent is administered as a series of two or more doses administered over one or more days.

[0177] In certain embodiments, a pharmaceutical agent of the present invention is administered to a patient between about 0.1% and 500%, more preferably between about 25% and 75% of an established human dosage. Where no human dosage is established, a suitable human dosage may be inferred from ED_{50} or ID_{50} values, or other appropriate values derived from *in vitro* or *in vivo* studies.

[0178] In certain embodiments, a daily dosage regimen for a patient comprises an oral dose of between 0.1 mg and 2000 mg of a compound of the present invention. In certain embodiments, a daily dosage regimen is administered as a single daily dose. In certain embodiments, a daily dosage regimen is administered as two, three, four, or more than four doses.

[0179] In certain embodiments, a pharmaceutical agent of the present invention is administered by continuous intravenous infusion. In certain of such embodiments, from 0.1 mg to 500 mg of a composition of the present invention is administered per day.

[0180] In certain embodiments, a pharmaceutical agent of the invention is administered for a period of continuous therapy. For example, a pharmaceutical agent of

the present invention may be administered over a period of days, weeks, months, or years.

[0181] Dosage amount, interval between doses, and duration of treatment may be adjusted to achieve a desired effect. In certain embodiments, dosage amount and interval between doses are adjusted to maintain a desired concentration on compound in a patient. For example, in certain embodiments, dosage amount and interval between doses are adjusted to provide plasma concentration of a compound of the present invention at an amount sufficient to achieve a desired effect. In certain of such embodiments the plasma concentration is maintained above the minimal effective concentration (MEC). In certain embodiments, pharmaceutical agents of the present invention are administered with a dosage regimen designed to maintain a concentration above the MEC for 10-90% of the time, between 30-90% of the time, or between 50-90% of the time.

[0182] In certain embodiments in which a pharmaceutical agent is administered locally, the dosage regimen is adjusted to achieve a desired local concentration of a compound of the present invention.

[0183] In certain embodiments, a pharmaceutical agent may be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack may for example comprise metal or plastic foil, such as a blister pack. The pack or dispenser device may be accompanied by instructions for administration. The pack or dispenser may also be accompanied with a notice associated with the container in form prescribed by a governmental agency regulating the manufacture, use, or sale of pharmaceuticals, which notice is reflective of approval by the agency of the form of the drug for human or veterinary administration. Such notice,

for example, may be the labeling approved by the U.S. Food and Drug Administration for prescription drugs, or the approved product insert. Compositions comprising a compound of the invention formulated in a compatible pharmaceutical carrier may also be prepared, placed in an appropriate container, and labeled for treatment of an indicated condition.

[0184] In certain embodiments, a pharmaceutical agent is in powder form for constitution with a suitable vehicle, *e.g.*, sterile pyrogen-free water, before use.

Certain Combination Therapies

[0185] In certain embodiments, one or more pharmaceutical agents of the present invention are co-administered with one or more other pharmaceutical agents. In certain embodiments, such one or more other pharmaceutical agents are designed to treat the same disease or condition as the one or more pharmaceutical agents of the present invention. In certain embodiments, such one or more other pharmaceutical agents are designed to treat a different disease or condition as the one or more pharmaceutical agents of the present invention. In certain embodiments, such one or more other pharmaceutical agents are designed to treat an undesired effect of one or more pharmaceutical agents of the present invention. In certain embodiments, one or more pharmaceutical agents of the present invention is co-administered with another pharmaceutical agent to treat an undesired effect of that other pharmaceutical agent. In certain embodiments, one or more pharmaceutical agents of the present invention and one or more other pharmaceutical agents are administered at the same time. In certain embodiments, one or more pharmaceutical agents of the present invention and one or more other pharmaceutical agents are administered at the different times. In certain embodiments, one or more pharmaceutical agents of the present invention and one or

more other pharmaceutical agents are prepared together in a single formulation. In certain embodiments, one or more pharmaceutical agents of the present invention and one or more other pharmaceutical agents are prepared separately.

[0186] Examples of pharmaceutical agents that may be co-administered with a pharmaceutical agent of the present invention include, but are not limited to, analgesics (*e.g.*, acetaminophen); anti-inflammatory agents, including, but not limited to non-steroidal anti-inflammatory drugs (*e.g.*, ibuprofen, COX-1 inhibitors, and COX-2, inhibitors); salicylates; antibiotics; antivirals; antifungal agents; antidiabetic agents (*e.g.*, biguanides, glucosidase inhibitors, insulins, sulfonylureas, and thiazolidenediones); adrenergic modifiers; diuretics; hormones (*e.g.*, anabolic steroids, androgen, estrogen, calcitonin, progestin, somatostatin, and thyroid hormones); immunomodulators; muscle relaxants; antihistamines; osteoporosis agents (*e.g.*, biphosphonates, calcitonin, and estrogens); prostaglandins, antineoplastic agents; psychotherapeutic agents; sedatives; poison oak or poison sumac products; antibodies; and vaccines.

Certain Indications

[0187] In certain embodiments, the invention provides methods of treating a patient comprising administering one or more compounds of the present invention. Compounds of the present invention, including, but not limited to, pharmaceutically acceptable salts, solvates and hydrates, are expected to be effective in treating diseases or conditions that are mediated by HNF-4α. Therefore, in certain embodiments, compounds of the invention are effective in treating conditions that are mediated by HNF-4α, including, but not limited to, syndrome X, non-insulin dependent diabetes mellitus, cancer, obesity, cardiovascular disease and dyslipidemia. In certain

embodiments, a patient is treated prophylactically to reduce or prevent the occurrence of a condition.

[0188] In certain embodiments, the present invention provides a method of lowering blood glucose levels in a mammal by administering to the patient a pharmaceutically effective amount of at least one compound of the present invention. In certain embodiments, the patient is a mammal. In certain embodiments, the patient is a human.

[0189] In certain embodiments, the present invention provides a method of lowering plasma triglycerides levels in a patient by administering to the mammal a pharmaceutically effective amount of at least one compound of the present invention. In certain embodiments, the patient is a mammal. In certain embodiments, the patient is a human.

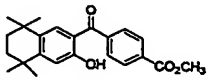
[0190] In certain embodiments, the present invention provides a method of increasing insulin levels in a patient by administering to the mammal a pharmaceutically effective amount of at least one compound of the present invention. In certain embodiments, the patient is a mammal. In certain embodiments, the patient is a human.

EXAMPLES

[0191] The following examples, including experiments and results achieved, are provided for illustrative purposes only and are not to be construed as limiting the present invention.

Example 1

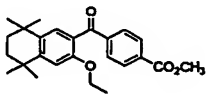
Methyl 4-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-hydroxy-2-naphthalenyl]benzoyl benzoate (Compound 101)



To a solution of 10.0 g (45.8 mmol) of 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-methoxy-2-naphthalene and 11.0 g (54.2 mmol) of 4-methoxycarbonyl benzoyl chloride in 100 ml of dry 1,2-dichloroethane in a round-bottomed flask was added portionwise 22.0 g (165.0 mmol) of $AlCl_3$ at 0° C. The mixture is warmed-up to room temperature and heated to reflux for 4 hours. After cooling down to room temperature, the deep reddish mixture was carefully poured on ice. The organic layer was separated and the aqueous layer extracted twice with CH_2Cl_2. The organic layers were combined, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude adduct was recrystallized from EtOAc/Hexane (1/9) to afford 8.6 g (25.9 mmol, yield: 55%) of Methyl 4-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-hydroxy-2-naphthalenyl]benzoyl benzoate as a bright yellow solid. ^1H NMR (500 MHz, $CDCl_3$) 11.5 (s, 1H), 8.19 (d, J=8.5 Hz, 2H), 7.82 (d, J=8.5 Hz, 2H), 7.43 (s, 1H), 7.01 (s, 1H), 3.99 (s, 3H), 1.67 (m, 4H), 1.31 (s, 6H), 1.16 (s, 6H).

Example 2

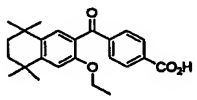
Methyl 4-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethoxy-2-naphthalenyl]benzoyl benzoate (Compound 102)



To a solution of methyl 4-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-hydroxy-2-naphthalenyl]benzoyl benzoate (0.9164 g, 2.5 mmol) in 20 mL of anhydrous DMF was sequentially treated with NaH (0.2 g, 5.0 mmol) and iodoethane (3.9 g, 25.0 mmol). The resulting mixture was heated to 60° C and stirred for 16 h. The reaction mixture was then quenched with 20 mL of water and extracted with ethyl acetate (150 mL). The ethyl acetate extract was washed with water (2 x 80 mL) and brine (80 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO2, 3 x 20 cm, 10% ethyl acetate in hexane as eluant) to give 0.8270 g (84%, theo. 0.9865 g) of product as a white solid. ^1H NMR (500 MHz, $CDCl_3$) 8.08 (d, *J*=8.2 Hz, 2H), 7.82 (d, *J*=8.2 Hz, 2H), 7.43 (s, 1H), 6.83 (s, 1H), 3.95 (s, 3H), 3.89 (q, *J*=7.0 Hz, 2H), 1.71 (m, 4H), 1.32 (s, 6H), 1.27 (s, 6H), 0.98 (t, *J*=7.0 Hz, 3H).

Example 3

4-[5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-3-ethyloxy-2-naphthalenyl]benzoyl benzoic acid (Compound 103)

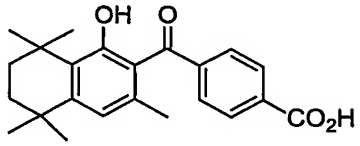


To a solution of methyl 4-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethyloxy-2-naphthalenyl]benzoyl benzoate (0.8270 g, 2.1 mmol) in 30 mL of a 3/1/1 ratio mixture of THF/MeOH/H_2O was treated with lithium hydroxide monohydrate (0.8796 g, 21.0 mmol). The resulting mixture was heated to reflux for 3 h. After TLC analysis indicating the completion of reaction. The mixture was acidified to pH=1 with 3.0 M aqueous HCl solution and extracted with ether (150 mL). The ether extract was washed with water (2 x

100 mL) and brine (100 mL). The ether layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was further purified by recrystallization from a 9/1 ratio of hexane/ether mixture to provided desired 0.6191 g (78%, theo. 0.7976 g) of product as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) 13.23(s, 1H), 8.02(d, J=8.2 Hz, 2H), 7.72(d, J=8.2 Hz, 2H), 7.34(s, 1H), 7.00(s, 1H), 3.92(q, J=7.0 Hz, 2H), 1.65(m, 4H), 1.29(s, 6H), 1.22(s, 6H), 0.84(t, J=7.0 Hz, 3H).

Example 4

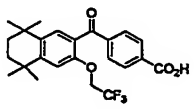
4-[5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-1-hydroxy-2-naphthalenyl]benzoyl benzoic acid (Compound 104)



Compound 104 was synthesized from methyl-4-[5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-1-hydroxy-2-naphthalenyl]benzoyl benzoate according to the procedure described in Example 3 using 3-methylphenol as starting material. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 11.5 (broad s, 1H), 8.20 (d, J = 8.5 Hz, 2H), 7.89 (d, J = 8.5 Hz, 1H), 6.81 (s, 1H), 2.20 (s, 3H), 1.68 (m, 4H), 1.35 (s, 6H), 1.30 (s, 6H).

Example 5

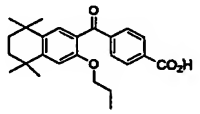
4-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-(1,1,1-trifluoroethoxy)-2-naphthalenyl]benzoyl benzoic acid (Compound 105)



Compound 105 was synthesized using the same synthetic procedure described in Example 3 with 1-bromo-2,2,2-trifluoroethane as alkylating reagent. ^{1}H NMR (500 MHz, DMSO-d_6) 13.20(br. s, 1H), 8.02(d, *J*=8.2 Hz, 2H), 7.73(d, *J*=8.2 Hz, 2H), 7.38(s, 1H), 7.16(s, 1H), 4.68(q, *J*=8.8 Hz, 2H), 1.66(m, 4H), 1.31(s, 6H), 1.22(s, 6H).

Example 6

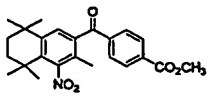
4-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-propoxy-2-naphthalenyl]benzoyl benzoic acid (Compound 106)



Compound 106 was synthesized using the same synthetic procedure described in Example 3 with propyl iodide as alkylating reagent. ^{1}H NMR (500 MHz, $CHCl_3$) 8.05 (d, *J*=8.3 Hz, 2H), 7.73 (d, *J*=8.3 Hz, 2H), 7.35 (s, 1H), 7.03 (s, 1H), 3.95 (q, *J*=7.0 Hz, 2H), 2.05 (m, 2H), 1.72 (m, 4H), 1.27 (s, 6H), 1.21 (s, 6H), 0.85 (t, *J*=7.0 Hz, 3H).

Example 7

Methyl 4-[5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-4-nitro-2-naphthalenyl]benzoyl benzoate (Compound 107)

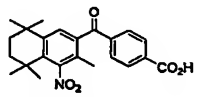


To a solution of methyl 4-[5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl]benzoyl benzoate (17.42 g, 47.8 mmol) in 250 mL of glacial acetic acid and 20 mL of concentrated H_2SO_4 was added slowly through an additional funnel of 140 mL of 90% fuming HNO_3. The resulting mixture was stirred at 23° C for 3 h. The

reaction mixture was then poured onto 500 g of ice-water mixture. The product crushed out of ice-water solution was collected by filtration. The crude product was taken into 500 mL of EtOAc and washed with water (3 x 300 mL) and brine (300 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 10 x 25 cm, 10% ethyl acetate in hexane as eluant) to give 15.66 g (80%, theo. 19.57 g) of product as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) 8.15 (d, *J*=8.5 Hz, 2H), 7.87 (d, *J*=8.5 Hz, 2H), 7.37 (s, 1H), 3.97 (s, 3H), 2.12 (s, 3H), 1.75 (m, 4H), 1.38 (s, 6H), 1.25 (s, 6H).

Example 8

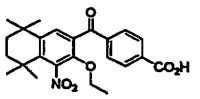
4-[5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-4-nitro-2-naphthalenyl]benzoyl benzoic acid (Compound 108)



Compound 108 was synthesized by saponification of methyl-4-[5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-4-nitro-2-naphthalenyl]benzoyl benzoate as described in Example 3. ^{1}H NMR (400 MHz, DMSO-d_6) 10.10 (s, 1H), 8.11(d, *J*=8.2 Hz, 2H), 7.83(d, *J*=8.2 Hz, 2H), 7.60(s, 1H), 1.98(s, 3H), 1.65(m, 4H), 1.31(s, 6H), 1.24(s, 6H).

Example 9

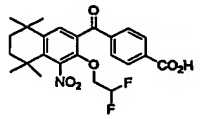
4-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethoxy-4-nitro-2-naphthalenyl]benzoyl benzoic acid (Compound 109)



Compound 109 was synthesized according to the synthetic scheme described in Example 3. ^{1}H NMR (500 MHz, $CDCl_3$) 8.11 (d, J = 8.55, 2H), 7.86 (d, J = 8.85, 2H), 7.68 (s, 1H), 3.67 (q, J = 6.7, 13.7, 2H), 1.71 (m, 4H), 1.31 (s, 6H), 1.27 (s, 6H), 0.85 (t, J = 7.0, 3H).

Example 10

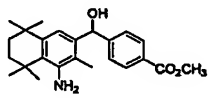
4-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-(2,2-difluoroethoxy)-4-nitro-2-naphthalenyl]benzoyl benzoic acid (Compound 110)



Compound 110 was synthesized according to the synthetic scheme described in Example 3. ^{1}H NMR (500 MHz, $CDCl_3$) 8.11 (d, J = 8.2, 2H), 7.87 (d, J = 8.2, 2H), 7.69 (s, 1H), 5.95 (m, 1H), 4.00 (m, 2H), 1.71 (m, 4H), 1.31 (s, 6H), 1.26 (s, 6H).

Example 11

Methyl 4-[5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-4-amino-2-naphthalenyl]hydroxymethyl benzoate (Compound 111)

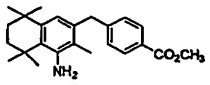


To a solution of methyl 4-[5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-4-amino-2-naphthalenyl]benzoyl benzoate (0.3016 g, 0.8 mmol) in 20 mL of a 1:1 ratio mixture of CH_2Cl_2/MeOH was treated with $NaBH_4$ (90.2 mg, 2.38 mmol) in one portion. The resulting mixture was stirred at 0° C for 30 min. The reaction mixture was quenched with

40 mL of water and extracted with EtOAc (100 mL). The extract was washed with water (3 x 50 mL) and brine (50 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, 3 x 20 cm, 25% ethyl acetate in hexane as eluant) to give product 0.25 g (82%, theo. 0.3031 g) as a white solid. ^1H NMR (500 MHz, $CDCl_3$) 8.01 (d, *J*=8.5 Hz, 2H), 7.44 (d, *J*=8.5 Hz, 2H), 6.76 (s, 1H), 6.02 (d, *J*=4.0 Hz, 1H), 3.91 (s, 3H), 3.86 (s, 2H), 2.16 (d, *J*=4.0 Hz, 1H), 2.03 (s, 3H), 1.72 (m, 2H), 1.61 (m, 2H), 1.45 (s, 3H), 1.44 (s, 3H), 1.24 (s, 3H), 1.17 (s, 3H).

Example 12

Methyl 4-[5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-4-amino-2-naphthalenyl]methyl benzoate (Compound 112)

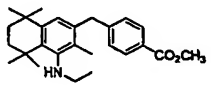


To a solution of methyl 4-[5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-4-amino-2-naphthalenyl]hydroxymethyl benzoate (0.2496 g, 0.65 mmol) in 20 mL of a 9:1 ratio mixture of EtOH/AcOH was treated with 10% palladium on carbon (50 mg). The resulting black suspension was stirred under hydrogen atmosphere (balloon pressure) at 23° C for 24 h. The catalyst was removed by filtering through a pad of celite and the celite cake was further rinsed with MeOH (80 mL) and CH_2Cl_2 (80 mL). The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 3 x 20 cm, 20% ethyl acetate in hexane as eluant) to give 0.1913 g (80%, theo. 0.2391 g) of product as a white solid. ^1H NMR (500 MHz, $CDCl_3$) 7.94

(d, *J*=8.5 Hz, 2H), 7.20 (d, *J*=8.5 Hz, 2H), 6.61 (s, 1H), 4.00 (s, 2H), 3.90 (s, 3H), 3.82 (s, 2H), 1.96 (s, 3H), 1.72 (m, 2H), 1.62 (m, 2H), 1.46 (s, 6H), 1.24 (s, 6H).

Example 13

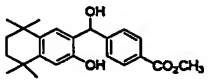
Methyl 4-[5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-4-ethylamino-2-naphthalenyl]methyl benzoate (Compound 113)



To a solution of methyl 4-[5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-4-amino-2-naphthalenyl]methyl benzoate (0.2170 g, 0.6 mmol) in 15 mL of CH_2Cl_2 was sequentially treated with acetaldehyde (0.33 mL, 5.9 mmol), 10 drops of AcOH and $NaCNBH_3$ (0.3709 g, 5.9 mmol). The resulting mixture was stirred at 0° C and allowed to slowly warm to 23° C and stirred for additional 16 h. The reaction mixture was quenched with 20 mL of water and extracted with EtOAc (100 mL). The extract was washed with water (3 x 50 mL) and brine (50 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, 3 x 20 cm, 10% ethyl acetate in hexane as eluant) to give 0.2175 g (93%, theo. 0.2337 g) of product as a white solid. ^1H NMR (500 MHz, $CDCl_3$) 7.95 (d, *J*=8.5 Hz, 2H), 7.21 (d, *J*=8.5 Hz, 2H), 6.76 (s, 1H), 3.98 (s, 2H), 3.91 (s, 3H), 3.30 (s, 1H), 2.85 (q, *J*=7.3 Hz, 2H), 2.11 (s, 3H), 1.71 (m, 2H), 1.62 (m, 2H), 1.44 (s, 6H), 1.23 (t, *J*=7.3 Hz, 3H), 1.22 (s, 6H).

Example 14

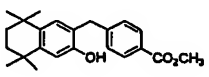
Methyl 4-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-hydroxy-2-naphthalenyl]hydroxymethyl benzoate (Compound 114)



To a solution of methyl 4-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-hydroxy-2-naphthalenyl]benzoyl benzoate (2.4424 g, 6.7 mmol) in 100 mL of a 1:1 ratio mixture of CH_2Cl_2/MeOH was treated with $NaBH_4$ (1.0086 g, 26.7 mmol) in one portion. The resulting mixture was stirred at 0° C for 30 min. The reaction mixture was quenched with 150 mL of saturated aqueous ammonium chloride solution and extracted with EtOAc (300 mL). The extract was washed with water (2 x 150 mL) and brine (150 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, 5 x 20 cm, 25% ethyl acetate in hexane as eluant) to give 2.46 g (100%, theo. 2.4558 g) of product as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) 8.03 (d, *J*=8.2 Hz, 2H), 7.48 (d, *J*=8.2 Hz, 2H), 7.09 (s, 1H), 6.83 (s, 1H), 6.81 (s, 1H), 6.00 (d, *J*=3.7 Hz, 1H), 3.91 (s, 3H), 3.03 (d, *J*=3.7 Hz, 1H), 1.64 (m, 4H), 1.25 (s, 3H), 1.24 (s, 3H), 1.18 (s, 3H), 1.15 (s, 3H).

Example 15

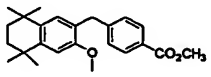
Methyl 4-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-hydroxy-2-naphthalenyl]methyl benzoate (Compound 115)



To a solution of methyl 4-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-hydroxy-2-naphthalenyl]hydroxymethyl benzoate (2.46 g, 6.7 mmol) in 150 mL of a 9:1 ratio mixture of EtOH/AcOH was treated with 10% palladium on carbon (500 mg). The resulting black suspension was stirred under hydrogen atmosphere (balloon pressure) at 23° C for 16 h. The catalyst was removed by filtering through a pad of celite and the celite cake was further rinsed with MeOH (100 mL) and CH_2Cl_2 (100 mL). The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 5 x 20 cm, 10% ethyl acetate in hexane as eluant) to give 2.2259 g (95%, theo. 2.3492 g) of product as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) 7.96 (d, *J*=8.2 Hz, 2H), 7.31 (d, *J*=8.2 Hz, 2H), 7.01 (s, 1H), 6.69 (s, 1H), 4.61 (s, 1H), 3.99 (s, 2H), 3.90 (s, 3H), 1.65 (m, 4H), 1.24 (s, 6H), 1.21 (s, 6H).

Example 16

Methyl 4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-methoxy-2-naphthalenyl)methyl]benzoate (Compound 116)

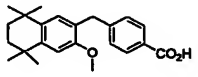


To a solution of methyl 4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-hydroxy-2-naphthalenyl)methyl] benzoate (0.1987 g, 0.56 mmol) in 10 mL of anhydrous DMF was sequentially treated with NaH (45 mg, 1.1 mmol) and iodomethane (0.24 g, 1.7 mmol). The resulting mixture was stirred at 23° C for 2 h. The reaction mixture was then quenched with 30 mL of water and extracted with ethyl acetate (150 mL). The ethyl acetate extract was washed with water (2 x 80 mL) and brine (80 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 3 x 20 cm, 2 to 5% ethyl acetate in

hexane as gradient eluant) to give 0.1805 g (87%, theo. 0.2066 g) of product as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) 7.94 (d, *J*=8.24 Hz, 2H), 7.29 (d, *J*=8.2 Hz, 2H), 6.98 (s, 1H), 6.75 (s, 1H), 3.96 (s, 2H), 3.90 (s, 3H), 3.77 (s, 3H), 1.66 (m, 4H), 1.29 (s, 6H), 1.20 (s, 6H).

Example 17

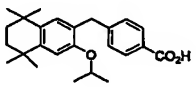
4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-methoxy-2-naphthalenyl)methyl]benzoic acid (Compound 117)



Compound 117 was synthesized from methyl 4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-methoxy-2-naphthalenyl)methyl]benzoate according to the procedure described for Example 3 using iodomethane as alkylating reagent. ^{1}H NMR (500 MHz, DMSO-d_6) 12.74(s, 1H), 7.81(d, *J*=8.24 Hz, 2H), 7.29(d, *J*=8.2 Hz, 2H), 7.08(s, 1H), 6.79(s, 1H), 3.87(s, 2H), 3.71(s, 3H), 1.58(m, 4H), 1.22(s, 6H), 1.15(s, 6H).

Example 18

4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-*iso*-propoxy-2-naphthalenyl)methyl]benzoic acid (Compound 118)

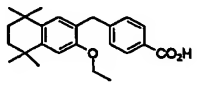


Compound 116 was synthesized from methyl 4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3- iso-propoxy -2-naphthalenyl)methyl]benzoate according to the procedure described in Example 3 using 2-iodopropane as alkylating reagent. ^{1}H NMR (500 MHz, DMSO-d_6) 12.74(s, 1H), 7.81(d, *J*=8.2 Hz, 2H), 7.31(d, *J*=8.2 Hz, 2H), 7.12(s, 1H), 6.75(s, 1H),

4.54(heptet, *J*=6.1 Hz, 2H), 3.84(s, 2H), 1.58(m, 4H), 1.19(s, 6H), 1.17(s, 6H), 1.15(d, *J*=6.1 Hz, 6H).

Example 19

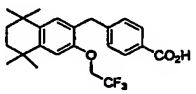
4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethoxy-2-naphthalenyl)methyl]benzoic acid (Compound 119)



Compound 119 was synthesized from methyl 4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3- ethoxy-2-naphthalenyl)methyl]benzoate according to the procedure described in Example 3 using iodoethane as alkylating reagent. ^{1}H NMR (500 MHz, DMSO-d_6) 12.74(s, 1H), 7.81(d, *J*=8.2 Hz, 2H), 7.31(d, *J*=8.2 Hz, 2H), 7.11(s, 1H), 6.75(s, 1H), 3.94(q, *J*=7.0 Hz, 2H), 3.86(s, 2H), 1.58(m, 4H), 1.25(t, *J*=7.0 Hz, 3H), 1.20(s, 6H), 1.16(s, 6H).

Example 20

4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-(1,1,1-trifuoroethoxy)-2-naphthalenyl)methyl]benzoic acid (Compound 120)

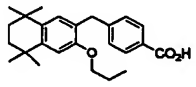


Compound 120 was synthesized from methyl 4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-(1,1,1-trifluoroethoxy)-2-naphthalenyl)methyl]benzoate according to the procedure described in Example 3 using 1-bromo-2,2,2-trifluoroethane as alkylating reagent. ^{1}H NMR (500 MHz, DMSO-d_6) 12.75(s, 1H), 7.80(d, *J*=8.2 Hz, 2H), 7.30(d, *J*=8.2 Hz, 2H),

7.20(s, 1H), 6.90(s, 1H), 4.68(q, *J*=8.8 Hz, 2H), 3.89(s, 2H), 1.58(m, 4H), 1.22(s, 6H), 1.17(s, 6H).

Example 21

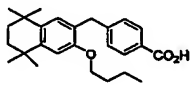
4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-propoxy-2-naphthalenyl)methyl]benzoic acid (Compound 121)



Compound 121 was synthesized from methyl 4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-propoxy-2-naphthalenyl)methyl]benzoate according to the procedure described in Example 3 using 1-iodopropane as alkylating reagent. ^{1}H NMR (500 MHz, DMSO-d_6) 12.74(s, 1H), 7.81(d, *J*=8.2 Hz, 2H), 7.30(d, *J*=8.2 Hz, 2H), 7.12(s, 1H), 6.75(s, 1H), 3.87(s, 2H), 3.84(t, *J*=6.2 Hz, 2H), 1.66(m, 2H), 1.58(m, 4H), 1.20(s, 6H), 1.16(s, 6H), 0.90(t, *J*=7.3 Hz, 3H).

Example 22

4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-butoxy-2-naphthalenyl)methyl]benzoic acid (Compound 122)

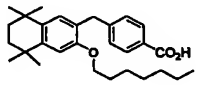


Compound 122 was synthesized from methyl 4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-butoxy-2-naphthalenyl)methyl]benzoate according to the procedure described in Example 3. ^{1}H NMR (500 MHz, DMSO-d_6) 12.74(s, 1H), 7.81(d, *J*=8.2 Hz, 2H),

7.29(d, *J*=8.2 Hz, 2H), 7.12(s, 1H), 6.75(s, 1H), 3.87(t, *J*=6.2 Hz, 2H), 3.86(s, 2H), 1.64-1.56(m, 6H), 1.33(m, 2H), 1.20(s, 6H), 1.16(s, 6H), 0.87(t, *J*=7.3 Hz, 3H).

Example 23

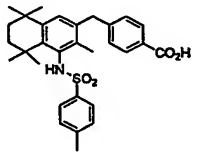
4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-heptoxy-2-naphthalenyl)methyl]benzoic acid (Compound 123)



Compound 123 was synthesized from methyl 4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-heptyloxy-2-naphthalenyl)methyl]benzoate according to the procedure described in Example 3. ^{1}H NMR (500 MHz, DMSO-d_6) 12.73(br. s, 1H), 7.80(d, *J*=8.2 Hz, 2H), 7.27(d, *J*=8.2 Hz, 2H), 7.13(s, 1H), 6.74(s, 1H), 3.86(m, 4H), 1.62-1.56(m, 6H), 1.26-1.13(m, 8H), 1.20(s, 6H), 1.17(s, 6H), 0.84(t, *J*=7.0 Hz, 3H).

Example 24

4-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-4-*p*-toluenesulfonylamido-2-naphthalenyl)methyl]benzoic acid (Compound 124)

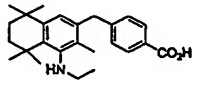


Compound 124 was synthesized from methyl 4-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-4-amino-2-naphthalenyl)methyl]benzoate according to the procedure described in Example 3 using *p*-toluenesulfonylchloride as reagent. ^{1}H NMR (500 MHz, DMSO-d_6) 12.82(s, 1H), 9.09(s, 1H), 7.85(d, *J*=8.2 Hz, 2H), 7.52(d, *J*=8.2 Hz, 2H),

7.19(d, *J*=8.2 Hz, 2H), 7.17(s, 1H), 7.14(d, *J*=8.2 Hz, 2H), 3.87(s, 2H), 2.30(s, 3H), 1.59-1.48(m, 4H), 1.42(s, 3H), 1.33(s, 6H), 1.20(s, 6H).

Example 25

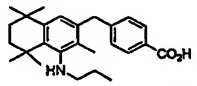
4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-methyl-4-ethylamino-2-naphthalenyl)methyl]benzoic acid (Compound 125)



Compound 123 was synthesized from methyl 4-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-4-amino-2-naphthalenyl)methyl]benzoate according to the procedure described in Example 3 using iodoethane as alkylating reagent. ^{1}H NMR (500 MHz, DMSO-d_6) 12.78(br. s, 1H), 7.84(d, *J*=8.2 Hz, 2H), 7.23(d, *J*=8.2 Hz, 2H), 6.82(s, 1H), 3.93(s, 2H), 2.69(q, *J*=7.0 Hz, 2H), 2.02(s, 3H), 1.63-1.51(m, 4H), 1.35(s, 6H), 1.16(s, 6H), 1.13(t, *J*=7.0 Hz, 3H).

Example 26

4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-methyl-4-propylamino-2-naphthalenyl)methyl]benzoic acid (Compound 126)

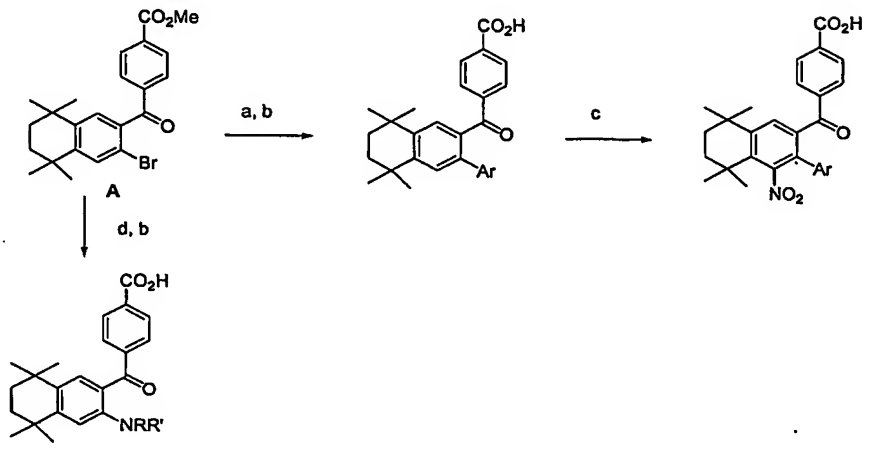


Compound 126 was synthesized from methyl 4-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-4-amino-2-naphthalenyl)methyl]benzoate according to the procedure described in Example 3 using iodopropane as alkylating reagent. ^{1}H NMR (500 MHz, DMSO-d_6) 12.76(br. s, 1H), 7.84(d, *J*=8.2 Hz, 2H), 7.23(d, *J*=8.2 Hz, 2H), 6.82(s, 1H),

3.93(s, 2H), 2.64(t, *J*=7.3 Hz, 2H), 2.02(s, 3H), 1.63-1.52(m, 6H), 1.35(s, 6H), 1.17(s, 6H), 0.93(t, *J*=7.3 Hz, 3H).

Derivatives with an aromatic group an amine functionality in the 3-position may be synthesized using the following procedures:

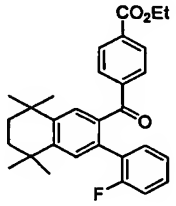
Scheme 5



Reagent and conditions: a) $ArB(OH)_2$, $Pd(PPh_3)_4$, toluene, ethanol, aq.2N Na_2CO_3, reflux. b) LiOH, THF/MeOH,room temp. c) HNO_3, H_2SO_4, AcOH, 0° C toroom temp. d) BINAP, Pd_2dba_3, amine, CsF, toluene, reflux.

Example 27

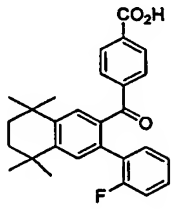
Ethyl 4-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-(2-fluorobenzene)-2-naphthalenyl]benzoyl benzoate (Compound 127)



In a two neck round bottomed flask containing a magnetic stir bar and equipped with a reflux condenser was introduced 429 mg (1.00 mmol) of ester A (Boehm and Al, *J. Med. Chem.*, 1994, **37**, 2930-2941), 208 mg (1.5 mmol, 1.5 equivalent) of 2-fluorobenzene boronic acid, 116 mg (0.10 mmol, 10 %/substrate) of tetrakistriphenylphosphine palladium ($Pd(PPh_3)_4$) followed by 5 ml of toluene, 5 ml of absolute EtOH and 1.0 ml of 2N aqueous Na_2CO_3 solution. The mixture was flushed with nitrogen and stirred at reflux overnight and then cooled to room temperature. Water was added and the solution was extracted with EtOAc (3 times). The organic layers were collected, washed with brine and dried over $MgSO_4$. After filtration and removal of the solvents, the crude ester was purified over silica gel column chromatography (eluent: 90/10 hexane/EtOAc) to afford 275 mg (0.6 mmol, yield: 60%) of the desired ethyl ester (compound 127). ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 8.5 Hz, 2H), 7.78 (d, J = 8.5 Hz, 2H), 7.47 (s, 1H), 7.38 (s, 1H), 7.27 (td, J = 6.5, 2.0 Hz, 1H), 7.17 (m, 1H), 7.07 (td, J = 7.5, 1.0 Hz, 1H), 6.88 (t, J = 9.5 Hz, 1H), 4.39 (dd, J = 14.3, 7.2 Hz, 2H), 1.75 (s, 4H), 1.41 (t, J = 7.0 Hz, 3H), 1.36 (s, 6H), 1.30 (s, 6H).

Example 28

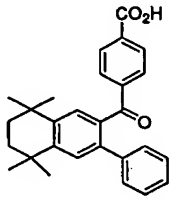
4-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-(2-fluorobenzene)-2-naphthalenyl]benzoyl benzoic acid (Compound 128)



In a round-bottomed flask was added 270 mg (0.588 mmol) of ethyl 4-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-(2-fluorobenzene)-2-naphthalenyl]benzoyl benzoate followed by 5 ml of THF, % ml of MeOH and 2 ml of 2N aqueous LiOH. The solution was stirred at room temperature until complexion and the solvents were removed under reduced pressure. The crude pasty mixture was acidified with 2N aqueous HCl (5 ml) and extracted twice with EtOAc. The organic layer was dried over $MgSO_4$, filtrated and concentrated. The crude acid was recrystallized from CH_3CN, to afford 190 mg (0.441 mmol, yield: 75%) of 4-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-(2-fluorobenzene)-2-naphthalenyl]benzoyl benzoic acid (Compound 128) as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 8.0 Hz, 2H), 7.80 (d, J = 8.0 Hz, 2H), 7.49 (s, 1H), 7.38 (s, 1H), 7.23 (m, 1H), 7.187 (m, 1H), 7.07 (td, J = 7.5, 1.0 Hz, 1H), 6.88 (t, J = 8.5 Hz, 1H), 1.76 (s, 4H), 1.36 (s, 6H), 1.31 (s, 6H).

Example 29

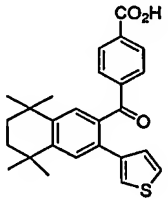
4-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-benzene-2-naphthalenyl)benzoyl benzoic acid (Compound 129)



Compound 129 was synthesized from A according to the procedure described in Example 28 using phenyl boronic acid as coupling reagent. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.95 (d, J = 8.0 Hz, 2H), 7.71 (d, J = 8.0 Hz, 2H), 7.50 (s, 1H), 7.39 (s, 1H), 7.09 (m, 4H), 7.05 (m, 1H), 5.87 (s, 1H), 1.77 (m, 4H), 1.37 (s, 6H), 1.34 (s, 3H).

Example 30

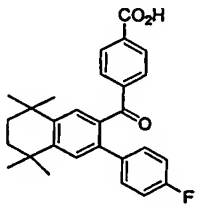
4-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-(3-thienyl)-2-naphthalenyl]benzoyl benzoic acid (Compound 130)



Compound 130 was synthesized from A according to the procedure described in Example 28 using 2-thiophen boronic acid as coupling reagent. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.98 (d, J = 8.5 Hz, 2H), 7.72 (d, J = 8.5 Hz, 2H), 7.46 (s, 1H), 7.42 (s, 1H), 7.11 (dd, J = 5.0, 3.0 Hz, 1H), 7.03 (dd, J = 3.0, 1.5 Hz, 1H), 6.94 (dd, J = 5.0, 1.5 Hz, 1H), 1.76 (m, 4H), 1.37 (s, 6H), 1.33 (s, 3H).

Example 31

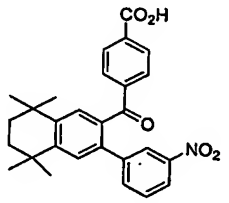
4-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-(4-fluorobenzene)-2-naphthalenyl]benzoyl benzoic acid (Compound 131)



Compound 131 was synthesized from A according to the procedure described in Example 28 using 4-fluorophenyl boronic acid as coupling reagent. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.98 (d, J = 8.4 Hz, 2H), 7.71 (d, J = 8.4 Hz, 2H), 7.48 (s, 1H), 7.34 (s, 1H), 7.16 (d, J = 8.5 Hz, 1H), 7.15 (d, J = 8.5 Hz, 1H), 6.88 (d, J = 8.5 Hz, 1H), 6.86 (d, J = 8.5 Hz, 1H), 1.76 (m, 4H), 1.37 (s, 6H), 1.32 (s, 3H).

Example 32

4-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-(3-nitrobenzene)-2-naphthalenyl]benzoyl benzoic acid (Compound 132)

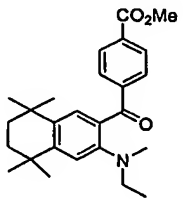


Example 32 was synthesized from A according to the procedure described in Example 28 using 3-nitrophenyl boronic acid as coupling reagent. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.11 (t, J = 2.0 Hz, 1H), 8.03 (d, J = 8.0 Hz, 2H), 8.02 (m, 1H), 7.77 (d, J = 8.0 Hz, 2H),

7.53 (s, 1H), 7.51 (m, 1H), 7.39 (d, J = 8.0 Hz, 1H), 7.37 (d, J = 8.0 Hz, 1H), 1.78 (m, 4H), 1.39 (s, 6H), 1.33 (s, 6H).

Example 33

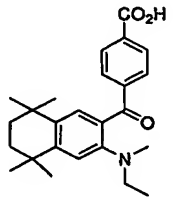
Methyl 4-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-(*NN*-methyl ethyl)-2-naphthalenyl] benzoyl benzoate (Compound 133)



In a pressure tube equipped with a magnetic bar was introduced successively 107 mg (0.249 mmol) of A, 25 mg (0.027 mmol) of Pd_2dba_3, 36 mg (0.058 mmol) of BINAP, 2.5 ml of dry toluene and 243 mg (0.746 mmol) of Cs_2CO_3. The tube was flushed with nitrogen, sealed and heated to 100° C overnight. After cooling to room temperature, water was added and the mixture was extracted with EtOAc. The organic layers were collected, washed with water and brine, dried over $MgSO_4$ and filtrated. After removal of the solvents, the crude oil was purified over silica gel column chromatography top afford 65 mg (0.159 mmol, yield: 64 %) of methyl 4-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-(NN-methyl ethyl)-2-naphthalenyl] benzoyl benzoate as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.05 (d, J = 8.3 Hz, 2H), 7.83 (d, J = 8.3 Hz, 2H), 7.31 (s, 1H), 6.93 (s, 1H), 3.94 (s, 3H), 2.86 (dd, J = 14.1, 7.0 Hz, 2H), 2.51 (s, 3H), 1.69 (m 4H), 1.32 (s, 6H), 1.24 (s, 6H), 0.81 (t, J = 6.9 Hz, 3H).

Example 34

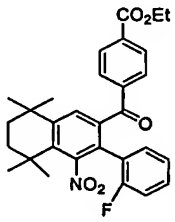
4-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-(*NN*-methyl ethyl)-2-naphthalenyl] benzoyl benzoic acid (Compound 134)



Saponification of 50 mg (0.123 mmol) of the ester x in the presence of 2 ml of THF, 2 ml of MeOH and 1 ml of 2N aqueous LiOH followed by acidic work-up and recrystallization from CH_3CN afford 25 mg (0.065 mmol, yield: 51 %) of the desired acid as a pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.21 (s, 1H), 8.09 (d, J = 7.8 Hz, 2H), 7.85 (d, J = 7.8 Hz, 2H), 7.39 (s, 1H), 3.82 (m, 23H), 3.34 (s, 3H), 1.72 (m 4H), 1.38 (s, 6H), 1.32 (m, 3H), 1.20 (s, 6H).

Example 35

Methyl-4-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-(2-fluorobenzene)-2-naphthalenyl]benzoyl benzoate (Compound 135)

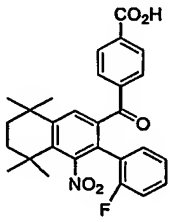


Compound 135 was synthesized according to the procedure used in the synthesis of Example 8. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.04 (d, J = 8.1Hz, 2H), 7.70 (d, J = 8.1 Hz,

2H), 7.55 (s, 1H), 7.24 (m, 1H), 7.14 (t, J = 7.4 Hz, 1H), 7.02 (t, J = 7.4 Hz, 1H), 6.86 (t, J = 7.4 Hz, 1H), 4.39 (dd J = 14.4, 7.2 Hz, 2H), 1.72 (m 4H), 1.42 (s, 6H), 1.34 (s, 6H), 1.31 (t, J = 7.2 Hz, 3H).

Example 36

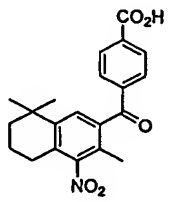
Methyl-4-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-(2-fluorobenzene)-2-naphthalenyl]benzoyl benzoic acid (Compound 136)



Compound 136 was synthesized from Methyl-4-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-(2-fluorobenzene)-2-naphthalenyl]benzoyl benzoate according to the nitration procedure used in the synthesis of Example 8 and the saponification procedure used in Example 3. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.08 (d, J = 8.5 Hz, 2H), 7.72 (d, J = 8.5 Hz, 2H), 7.58 (s, 1H), 7.23 (m, 1H), 7.14 (t, J = 9.5 Hz, 1H), 7.03 (t, J = 8.0 Hz, 1H), 6.86 (t, J = 9.5 Hz, 1H), 1.82 (m 4H), 1.43 (s, 3H), 1.40 (s, 3H), 1.36 (s, 3H), 1.34 (s, 3H).

Example 37

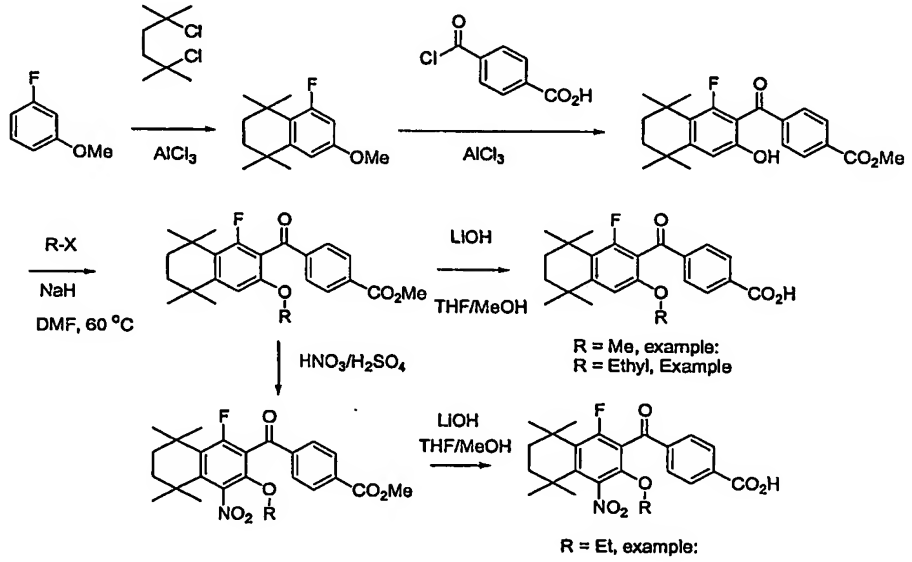
4-[5,6,7,8-tetrahydro-3,8,8-tetramethyl-4-nitro-2-naphthalenyl]benzoyl benzoic acid (Compound 137)



Compound 137 was synthesized from Methyl-4-[5,6,7,8-tetrahydro-3,5,5-tetramethyl-2-naphthalenyl]benzoyl benzoate according to the nitration procedure used in the synthesis in Example 8 and the saponification procedure used in Example 3. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.22 (d, J = 8.2 Hz, 2H), 7.89 (d, J = 8.2 Hz, 1H), 7.39 (s, 1H), 2.69 (t, J = 6.7 Hz, 2H), 2.19 (s, 3H), 1.83 (m, 2H), 1.75 (m, 2H), 1.26 (s, 6H).

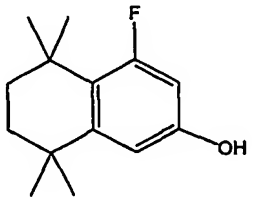
Introduction of substitutions in position 6 of structure 1 may be used using the following scheme:

Scheme 6



Example 38

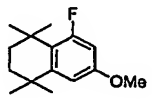
(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-hydroxy-6-fluoro)-naphthalene (Compound 138)



To a mixture of 2.7 g (2.2 ml, 24 mmol) of 3-fluorophenol and 5.29 g (29 mmol) of 2,5-dichloro-2,5-dimethylhexane in 100 ml of dry CH_2Cl_2 was added carefully 3.8 g (28.8 mmol) of $AlCl_3$ portionwise at 0° C. The mixture was stirred until complexion (TLC monitored) and poured into ice. After extraction with CH_2Cl_2, the organic layers were collected and washed with water and brine, then dried over $MgSO_4$. After filtration, the precipitate was purified over silica gel column chromatography top afford 2.9 g (13.0 mmol, yield: 54 %) of [5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-hydroxy-6-fluoro]naphthalene as a white solid. ^1H NMR (500 MHz, $CDCl_3$) δ: 6.58 (dd, $J = 2.7$, 0.9 Hz, 1H), 6.35 (dd, $J = 13.4$, 2.7 Hz, 1H), 4.58 (broad s, 1H), 1.66 (m, 4H), 1.34 (s, 3H), 1.33 (s, 3H), 1.25 (s, 6H).

Example 39

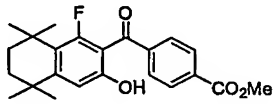
(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-methoxy-1-fluoro)-naphthalene (Compound 139)



A mixture of 2.88 g (12.9 mmol) of (5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-hydroxy-6-fluoro)-naphthalene, 1.1 ml (2.2 g, 15.5 mmol) of CH_3I and 6.3 g (19.0 mmol) of Cs_2CO_3 in 10 ml of dry DMF was stirred overnight at room temperature. 50 ml of a 95/5 mixture of hexane/EtOAc was added and the suspension was filtrated over a silica gel plug. The plug was washed 2 times and the solvent were removed under reduced pressure to afford the desired (5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-methoxy-6-fluoro)-naphthalene directly used in the next step. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.68 (dd, J = 2.6, 0.9 Hz, 1H), 6.41 (dd, J = 13.2, 2.6 Hz, 1H), 3.76 (s, 3H), 1.67 (m, 4H), 1.35 (s, 3H), 1.34 (s, 3H), 1.27 (s, 6H).

Example 40

Methyl-4-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-hydroxy-6-fluoro-2-naphthalenyl]benzoyl benzoate (Compound 140)

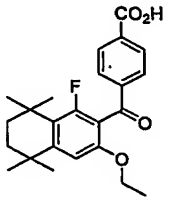


To a mixture of 700 mg (2.9 mmol) of (5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-methoxy-6-fluoro)-naphthalene, 600 mg (2.9 mmol) of methyl-4-chlorocarbonylbenzoate in 10 ml of dry 1,2-dichloroethane was added slowly 1.5 g (11.6 mmol) of $AlCl_3$. The mixture was stirred at reflux until complexion (TLC monitored) and poured into ice. After work-up the organic layers were dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude oil was purified over silica gel column chromatography (eluent: 90/10 hexane/EtOAc) to afford 330 mg (0.86 mmol, yield: 30 %) of methyl-4-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-hydroxy-6-fluoro-2-naphthalenyl]benzoyl benzoate as a yellow pasty oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ:

10.75 (s, 1H), 8.13 (d, J = 8.5 Hz, 2H), 7.72 (d, J = 8.5 Hz, 2H), 6.86 (d, J = 1.2 Hz, 1H), 3.96 (s, 3H), 1.66 (m, 4H), 1.31 (s, 6H), 1.27 (s, 3H), 1.26 (s, 3H).

Example 41

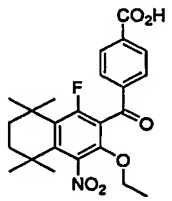
4-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethoxy-6-fluoro-2-naphthalenyl]benzoyl benzoic acid (Compound 141)



Compound 141 was synthesized from methyl-4-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-hydroxy-6-fluoro-2-naphthalenyl]benzoyl benzoate according to the procedure described in Example 3 using iodoethane as alkylating reagent. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.18 (d, J = 8.3 Hz, 2H), 7.94 (d, J = 8.3 Hz, 1H), 6.69 (s, 1H), 3.96 (dd, J = 13.9, 7.0 Hz, 2H), 1.67 (m, 4H), 1.33 (s, 6H), 1.31 (s, 6H), 1.13 (t, J = 7.0 Hz, 3H).

Example 42

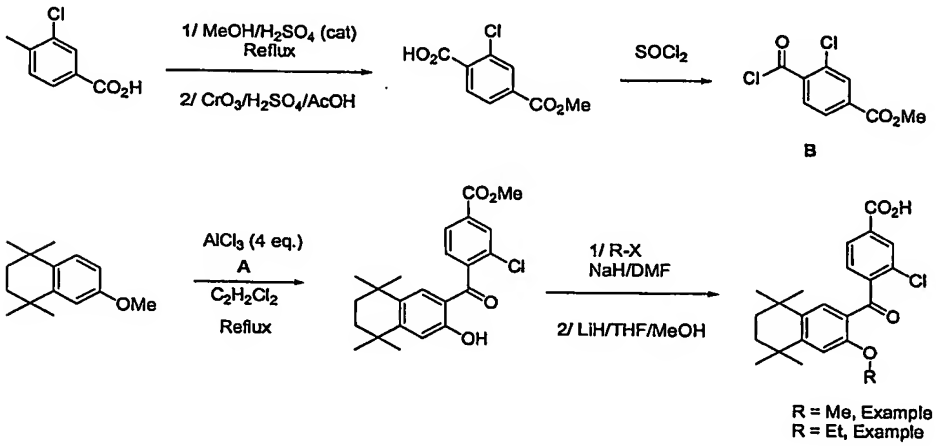
4-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethoxy-4-nitro-6-fluoro-2-naphthalenyl]benzoyl benzoic acid (Compound 142)



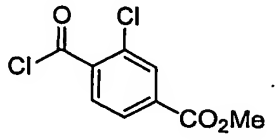
Compound 142 was synthesized from methyl-4-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-hydroxy-6-fluoro-2-naphthalenyl]benzoyl benzoate according to the nitration procedure described in Example 1 and the saponification procedure described in Example 3. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.23 (d, J = 8.4 Hz, 2H), 7.95 (d, J = 8.4 Hz, 1H), 3.87 (dd, J = 14.0, 7.0 Hz, 2H), 1.75 (m, 2H), 1.69 (m, 2H), 1.38 (s, 6H), 1.36 (s, 3H), 1.35 (s, 3H), 1.08 (t, J = 7.1 Hz, 3H).

Introduction of substituents in the R_4 position of compounds of structure I may be used according to the following scheme:

Scheme 7



methyl-3-chloro-4-chlorocarbonylbenzoate **B**.

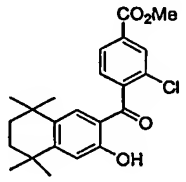


To a solution of 5.1 g (23.7 mmol) 3-chloro-4-methylcarbonylbenzoic acid in 20 ml of toluene, was added 10 ml of thionyl chloride and 0.5 ml of DMF. The mixture was stirred at reflux for 3 hours and cooled down to room temperature. The solvents and

excess of thionyl chloride were removed under reduced pressure and the crude acyl chloride recrystallized from hexane to afford 5.1 g (21.8 mmol, yield: 92 %) of methyl-3-chloro-4-chlorocarbonylbenzoate **B** as a white crystal.

Example 43

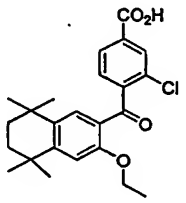
Methyl 3-chloro-4-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-hydroxy-2-naphthalenyl]benzoyl benzoate (Compound 143)



To a solution of 1.90 g (25.8 mmol) of 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-methoxy-2-naphthalene and 1.93 g (54.2 mmol) of 3-chloro-4-methoxycarbonyl benzoyl chloride in 50 ml of dry 1,2-dichloroethane in a round-bottomed flask was added portionwise 3.4 g (25.8 mmol) of $AlCl_3$ at 0° C. The mixture is warmed-up to room temperature and heated to reflux for 4 hours. After cooling down to room temperature, the deep reddish mixture was carefully poured on ice. The organic layer was separated and the aqueous layer extracted twice with CH_2Cl_2. The organic layers were combined, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude adduct was purified over silica gel column chromatography (eluent: EtOAc/Hexane, 1/9) to afford 2.6 g (7.2.9 mmol, yield: 925%) of methyl 3-chloro-4-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-hydroxy-2-naphthalenyl]benzoyl benzoate as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 11.42 (s, 1H), 8.18 (s, 1H), 8.06 (d, J = 7.9 Hz, 2H), 7.43 (d, J = 7.9 Hz, 2H), 7.09 (s, 1H), 6.99 (s, 1H), 3.98 (s, 3H), 1.78 (m 4H), 1.29 (s, 6H), 1.07 (s, 6H).

Example 44

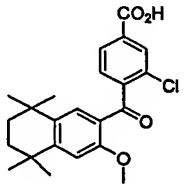
3-chloro-4-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethoxy-2-naphthalenyl]benzoyl benzoic acid (Compound 144)



Compound 144 was synthesized from methyl 3-chloro-4-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-hydroxy-2-naphthalenyl]benzoyl benzoate according to the procedure described in Example 3 using iodoethane as alkylating reagent. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.12 (broad s, 1H), 8.00 (broad d, J = 8.0 Hz, 1H), 7.91 (s, 1H), 7.39 (d, J = 8.0 Hz, 1H), 6.74 (s, 1H), 7.11 (s, 1H), 3.79 (dd, J = 14.0, 7.0 Hz, 1H), 1.70 (m, 4H), 1.31 (s, 6H), 1.29 (s, 6H), 0.82 (t, J = 7.0 Hz, 3H).

Example 45

3-chloro-4-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-methoxy-2-naphthalenyl]benzoyl benzoic acid (Compound 145)

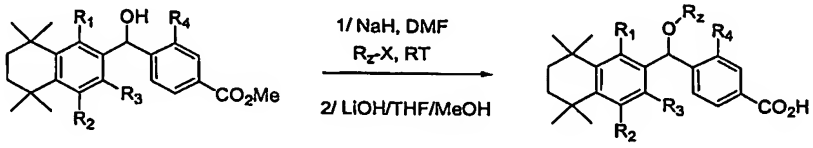


Example 45 was synthesized from methyl 3-chloro-4-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-hydroxy-2-naphthalenyl]benzoyl benzoate according to the procedure described in Example 3 using iodomethane as alkylating reagent. ^{1}H NMR (400 MHz,

$CDCl_3$) δ: 8.13 (d, J = 1.5 H, 1H), 8.02 (dd, J = 8.0, 1.5 Hz, 1H), 7.81 (s, 1H), 7.41 (d, J = 8.0 Hz, 1H), 6.80 (s, 1H), 3.56 (s, 3H), 1.71 (m, 4H), 1.31 (s, 6H), 1.29 (s, 6H).

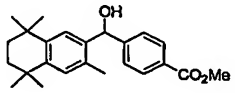
Compounds of the generic formula **16** may be synthesized according to the following scheme:

Scheme 8



Example 46

Methyl 4-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)hydroxymethyl] benzoate (Compound 146)

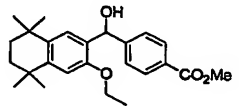


To a solution of 2 g (5.5 mmol) of methyl 4-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-3-methyl-2naphthalenyl)]benzoyl benzoate in 10 ml of methanol, was added 415 mg (11.0 mmol) of $NaBH_4$ portionwise at 0° C. The mixture was stirred at this temperature until complexion, the mixture was worked-up and the residual oil was purified by crystallization from hexanes to afford 1.97 g (5.4 mmol, yield: 98 %) of methyl 4-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)hydroxymethyl] benzoate as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.03 (d, J = 8.0 Hz, 2H), 7.45 (d, J = 8.0

Hz, 2H), 7.13 (s, 1H), 6.67 (s, 1H), 5.88 (broad s, 1H), 3.85 (s, 3H), 2.2 (s, 3H), 1.71 (m, 4H), 1.31 (s, 6H), 1.29 (s, 6H).

Example 47

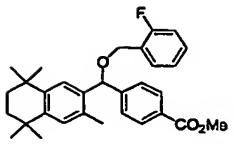
Methyl 4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethoxy-2-naphthalenyl)hydroxymethyl] benzoate (Compound 147)



To a solution of 3 g (7.6 mmol) of methyl 4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethoxy-2naphthalenyl)]benzoyl benzoate in 15 ml of methanol, was added 575 mg (15.2 mmol) of $NaBH_4$ portionwise at 0° C. The mixture was stirred at this temperature until complexion, the mixture was worked-up and the residual oil was purified by crystallization from hexanes to afford 2.86 g (7.2 mmol, yield: 95 %) of methyl 4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethoxy-2-naphthalenyl)hydroxymethyl] benzoate as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ: 8.05 (d, J = 8.0 Hz, 2H), 7.46 (d, J = 8.0 Hz, 2H), 7.15 (s, 1H), 6.62 (s, 1H), 5.92 (broad s, 1H), 3.92 (m, 1H), 3.88 (m, 1H), 3.83 (s, 3H), 2.19 (s, 3H), 1.70 (m, 4H), 1.32 (t, J = 7.0 Hz, 3H), 1.25 (s, 3H), 1.24 (s, 3H), 1.18 (s, 3H), 1.12 (s, 3H).

Example 48

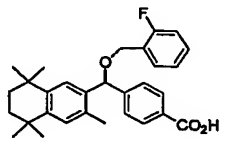
Methyl 4-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)(2-fluorobenzyloxy)methyl] benzoate (Compound 148)



A dispersion of sodium hydride in oil (200 mg, 60%wt, 5 mmol) was added to a suspension of methyl 4-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)hydroxymethyl] benzoate in 10 mL of THF atroom temp. The mixture was stirred for 20 min before addition of 2-fluorobenzyl bromide (0.8 mL, 6.3 mmol). The mixture was stirred overnight and then 25 mL of 1M aqueous HCl solution was slowly added. The mixture was extracted with 75 mL of EtOAc, and the organic layer was dried and concentrated to leave a residue that was purified by silica gel chromatography (10% followed by 25% EtOAc/hexane) to afford 580 mg (39%) of methyl 4-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-3-methyl-2-naphthalenyl)(2-fluorobenzyloxy)methyl] benzoate as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.05 (d, J = 8.3 Hz, 2H), 7.44 (m, 1H), 7.43 (d, J = 8.3 Hz, 2H), 7.22 (m, 1H), 7.21 (s, 1H), 7.15 (ddd, J = 1, 8.5, 8.5 Hz, 1H), 7.02 (s, 1H), 7.01 (dd, J = 8.5, 8.5 Hz, 1H), 5.67 (s, 1H), 4.60 (ABq, JAB = 11.7 Hz, 2H), 2.18 (s, 3H), 1.67 (s, 4H), 1.29 (s, 6H), 1.25 (s, 3H), 1.13 (s, 3H).

Example 49

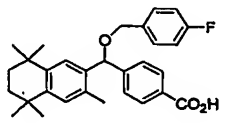
4-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)(2-fluorobenzyloxy)methyl]benzoic acid (Compound 149)



To a solution of methyl 4-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)(2-fluorobenzyloxy)methyl] benzoate (580 mg, 1.2 mmol) in 2 mL of THF was added 2 mL of MeOH, 1 mL of water, and lithium hydroxide monohydrate (150 mg, 3.6 mmol). The mixture was stirred overnight at room temperature before treatment with 10 mL of 1M aqueous HCl solution and extraction with 25 mL of EtOAc. The organic layer was dried and concentrated to leave a crude solid product that was recrystallized from CH_3CN to yield 348 mg (62%) of 4-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)(2-fluorobenzyloxy)methyl]benzoic acid as a white solid. ^{1}H NMR (500 MHz, CDCl3) δ: 8.07 (d, J = 8.3 Hz, 2H), 7.47 (m, 1H), 7.46 (d, J = 8.3 Hz, 2H), 7.28 (m, 1H), 7.26 (s, 1H), 7.14 (ddd, J = 1, 8.5, 8.5 Hz, 1H), 7.05 (s, 1H), 7.04 (dd, J = 8.5, 8.5 Hz, 1H), 5.64 (s, 1H), 4.63/4.57 (ABq, JAB = 11.7 Hz, 2H), 2.20 (s, 3H), 1.66 (s, 4H), 1.27 (s, 6H), 1.24 (s, 3H), 1.19 (s, 3H).

Example 50

4-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)(4-fluorobenzyloxy)methyl]benzoic acid (Compound 150)

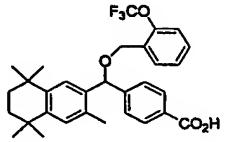


Compound 150 was synthesized from methyl 4-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)(2-fluorobenzyloxy)methyl] benzoate according to the procedure described in Example 49 using 4-fluorobenzyl bromide as alkylating reagent. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.06 (d, J = 8.5 Hz, 2H), 7.44 (d, J = 8.5 Hz, 2H), 7.33 (d, J = 8.6 Hz, 1H), 7.32 (d, J = 8.9 Hz, 1H), 7.27 (s, 1H), 7.05 (s, 1H), 7.04 (d, J = 8.5,

1H), 7.03 (d, J = 8.9, 1H), 5.58 (s 1H), 4.54/4.45 (ABq, JAB = 11.6 Hz, 2H), 2.16 (s, 3H), 1.67 (s, 4H), 1.27 (s, 3H), 1.26 (s, 3H), 1.25 (s, 3H), 1.20 (s, 3H).

Example 51

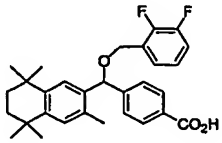
4-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)(2-trifluoromethoxybenzyloxy) methyl] benzoic acid (Compound 151)



Compound 151 was synthesized from methyl 4-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)(2-fluorobenzyloxy)methyl] benzoate according to the procedure described in Example 47 using 2-trifluoromethoxybenzyl bromide as alkylating reagent. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.09 (d, J = 8.3 Hz, 2H), 7.61 (dd, J = 2.0, 7.4 Hz), 7.48 (d, J = 8.3 Hz, 2H), 7.33 (m, 2H), 7.28 (s, 1H), 7.26 (m, 1H), 7.07 (s, 1H), 5.65 (s, 1H), 4.64/4.61 (ABq, JAB = 12.2 Hz, 2H), 2.20 (s, 3H), 1.67 (s, 4H), 1.27 (s, 6H), 1.25 (s, 3H), 1.20 (s, 3H).

Example 52

4-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)(2,3-difluorobenzyloxy)methyl]benzoic acid (Compound 152)

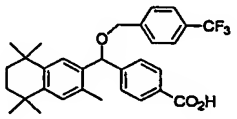


Compound 152 was synthesized from methyl 4-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)(2-fluorobenzyloxy)methyl] benzoate according to the

procedure described for Example 49 using 2,3-difluorobenzyl bromide as alkylating reagent. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.08 (d, J = 8.2 Hz, 2H), 7.46 (d, J = 8.5 Hz, 2H), 7.26 (s, 1H), 7.23 (m, 1H), 7.08 (m, 2H), 7.06 (s, 1H), 5.65 (s, 1H), 4.65/4.59 (ABq, JAB = 12 Hz, 2H), 2.20 (s, 3H), 1.67 (s, 4H), 1.27 (s, 6H), 1.25 (s, 3H), 1.20 (s, 3H).

Example 53

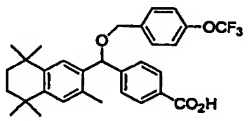
4-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)(4-trifluoromethylbenzyloxy) methyl]benzoic acid (Compound 153)



Compound 153 was synthesized from methyl 4-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)(2-fluorobenzyloxy)methyl] benzoate according to the procedure described for Example 49 using 4-trifluoromethylbenzyl bromide as alkylating reagent. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.08 (d, J = 8.2 Hz, 2H), 7.61 (d, J = 8.2 Hz, 2H), 7.48 (d, J = 8.5 Hz, 2H), 7.46 (d, J = 8.2 Hz, 2H), 7.31 (s, 1H), 7.05 (s, 1H), 5.61 (s, 1H), 4.64/4.55 (ABq, JAB = 12.5 Hz, 2H), 2.17 (s, 3H), 1.67 (s, 4H), 1.27 (s, 3H), 1.27 (s, 3H), 1.26 (s, 3H), 1.21 (s, 3H).

Example 54

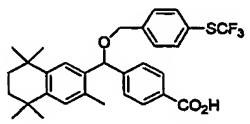
4-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)(4-trifluoromethoxybenzyloxy)methyl] benzoic acid (Compound 154)



Compound 154 was synthesized from methyl 4-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)(2-fluorobenzyloxy)methyl] benzoate according to the procedure described in Example 49 using 4-trifluoromethoxybenzyl bromide as alkylating reagent. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.07 (d, J = 8.2 Hz, 2H), 7.45 (d, J = 8.5 Hz, 2H), 7.38 (d, J = 8.5 Hz, 2H), 7.28 (s, 1H), 7.20 (d, J = 8.2 Hz, 2H), 7.05 (s, 1H), 5.60 (s, 1H), 4.57/4.49 (ABq, JAB = 12 Hz, 2H), 2.17 (s, 3H), 1.67 (s, 4H), 1.27 (s, 3H), 1.26 (s, 3H), 1.25 (s, 3H), 1.20 (s, 3H).

Example 55

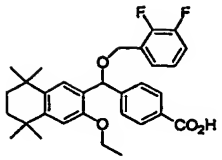
4-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)(4-trifluorothiomethoxybenzyloxy)methyl] benzoic acid (Compound 155)



Compound 155 was synthesized from methyl 4-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)(2-fluorobenzyloxy)methyl] benzoate according to the procedure described in Example 49 using 4-trifluorothiomethoxybenzyl bromide as alkylating reagent. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.06 (d, J = 8.1 Hz, 2H), 7.46 (d, J = 8.2 Hz, 2H), 7.39 (d, J = 8.2 Hz, 2H), 7.29 (s, 1H), 7.22 (d, J = 8.1 Hz, 2H), 7.03 (s, 1H), 5.62 (s, 1H), 4.58/4.45 (ABq, JAB = 12 Hz, 2H), 2.16 (s, 3H), 1.68 (s, 4H), 1.25 (s, 3H), 1.24 (s, 3H), 1.23 (s, 3H), 1.20 (s, 3H).

Example 56

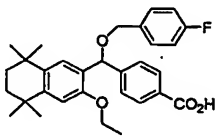
4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethoxy-2-naphthalenyl)(2,3-difluorobenzyloxy)methyl]benzoic acid (Compound 156)



Compound 156 was synthesized from methyl 4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethoxy-2-naphthalenyl)hydroxymethyl] benzoate according to the procedure described in Example 49 using 2,3-difluorobenzyl bromide as alkylating reagent. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.03 (d, J = 8.2 Hz, 2H), 7.54 (d, J = 8.2 Hz, 2H), 7.36 (s, 1H), 7.25 (m, 1H), 7.07 (m, 2H), 6.71 (s, 1H), 5.92 (s, 1H), 4.66/4.59 (ABq, JAB = 12 Hz, 2H), 4.00 (m, 2H), 1.65 (s, 4H), 1.37 (t, J = 7 Hz, 3H), 1.26 (s, 3H), 1.24 (s, 3H), 1.24 (s, 3H), 1.17 (s, 3H).

Example 57

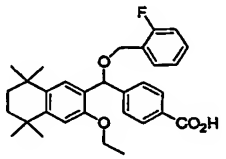
4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethoxy-2-naphthalenyl)(4-fluorobenzyloxy)methyl]benzoic acid (Compound 157)



Compound 157 was synthesized from methyl 4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethoxy-2-naphthalenyl)hydroxymethyl] benzoate according to the procedure described for Example 49 using 4-fluorobenzyl bromide as alkylating reagent. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.04 (d, J = 8.3 Hz, 2H), 7.55 (d, J = 8.8 Hz, 2H), 7.41 (s,1H), 7.34 (dd, J = 5.4, 8.3 Hz, 2H), 7.04 (dd, J = 8.8, 8.8 Hz, 2H), 6.72 (s, 1H), 5.88 (s, 1H), 4.55/4.49 (ABq, JAB = 11.5 Hz, 2H), 4.00 (m, 2H), 1.66 (s, 4H), 1.38 (t, J = 7 Hz, 3H), 1.28 (s, 3H), 1.27 (s, 3H), 1.25 (s, 3H), 1.19 (s, 3H).

Example 58

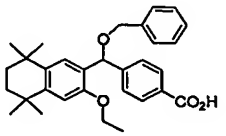
4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethoxy-2-naphthalenyl)(2-fluorobenzyloxy)methyl]benzoic acid (Compound 158)



Compound 158 was synthesized from methyl 4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethoxy-2-naphthalenyl)hydroxymethyl] benzoate according to the procedure described in Example 49 using 2-fluorobenzyl bromide as alkylating reagent. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.05 (d, J = 8.3 Hz, 2H), 7.57 (d, J = 8.8 Hz, 2H), 7.52 (ddd, J = 2.0, 7.4, 7.4, 1H), 7.42 (s, 1H), 7.28 (m, 1H), 7.15 (ddd, J = 1.0, 7.3, 7.3 Hz, 1H), 7.04 (ddd, J = 1.0, 8.3, 9.3 Hz, 1H), 6.73 (s, 1H), 5.94 (s, 1H), 4.67/4.59 (ABq, JAB = 12.2 Hz, 2H), 4.01 (m, 2H), 1.66 (s, 4H), 1.38 (t, J = 7 Hz, 3H), 1.28 (s, 3H), 1.27 (s, 3H), 1.25 (s, 3H), 1.20 (s, 3H).

Example 59

4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethoxy-2-naphthalenyl)(benzyloxy) methyl]benzoic acid (Compound 159)

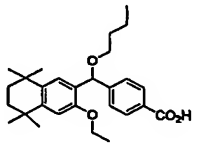


Compound 159 was synthesized from methyl 4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethoxy-2-naphthalenyl)hydroxymethyl] benzoate according to the procedure described in Example 49 using benzyl bromide as alkylating reagent. ^{1}H NMR (500 MHz, $CDCl_3$)

δ: 8.05 (d, J = 8.3 Hz, 2H), 7.57 (d, J = 8.3 Hz, 2H), 7.45 (s, 1H), 7.3-7.4 (m, 5H), 6.73 (s, 1H), 5.91 (s, 1H), 4.60/4.53 (ABq, JAB = 11.7 Hz, 2H), 4.00 (m, 2H), 1.67 (s, 4H), 1.37 (t, J = 7 Hz, 3H), 1.28 (s, 3H), 1.28 (s, 3H), 1.26 (s, 3H), 1.20 (s, 3H).

Example 60

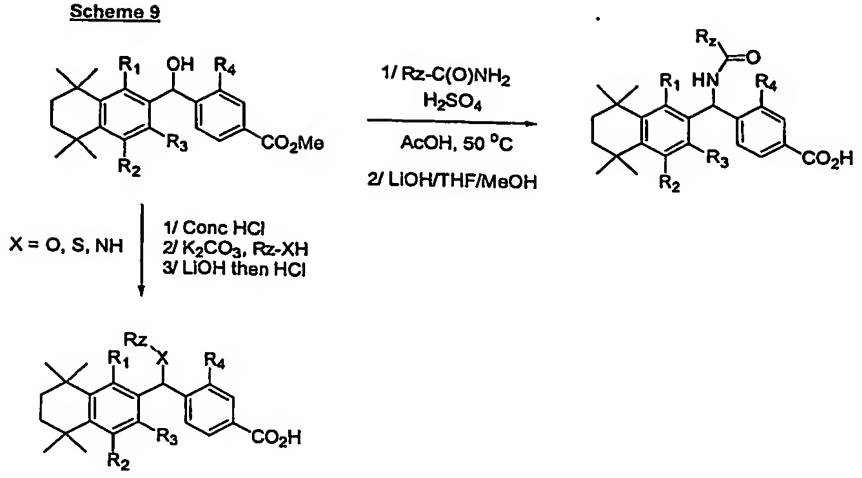
4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethoxy-2-naphthalenyl)(butyloxy)methyl]benzoic acid (Compound 160)



Compound 160 was synthesized from methyl 4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethoxy-2-naphthalenyl)hydroxymethyl] benzoate according to the procedure described in Example 49 using iodobutane as alkylating reagent. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.01 (d, J = 8.2 Hz, 2H), 7.51 (d, J = 8.2 Hz, 2H), 7.35 (s, 1H), 6.69 (s, 1H), 5.73 (s, 1H), 3.98 (m, 2H), 3.46 (m, 2H), 1.61 (m, 2H), 1.43 (m, 2H), 1.39 (t, J = 6.7 Hz, 3H), 1.26 (s, 3H), 1.26 (s, 3H), 1.25 (s, 3H), 1.23 (s, 3H), 1.18 (s, 3H), 0.92 (t, J = 7.3 Hz, 3H).

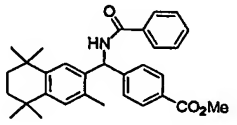
Compounds possessing an amide or an amine between both aromatic rings (R_6 = H, R_7 = amide or amine) may be synthesized via the following scheme.

Scheme 9



Example 61

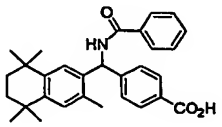
Methyl 4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-methyl-2-naphthalenyl)(benzamido) methyl]benzoate (Compound 161)



To a suspension of methyl 4-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)(hydroxymethyl] benzoate (50 mg, 0.14 mmol) in 1.5 mL of glacial acetic acid was added benzamide (290 mg, 2.3 mmol), followed by 5 drops of conc, H_2SO_4. The mixture was stirred and heated at 50° C overnight. After cooling to room temp., the mixture was diluted with water and extracted with Et_2O. The ether layer was dried and concentrated to leave a residue that was purified by silica gel chromatography (25% followed by 50% EtOAc/hexane) to afford 32 mg (48%) of methyl 4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-methyl-2-naphthalenyl)(benzamido)methyl]benzoate (compound 161) as a colorless oil.

Example 62

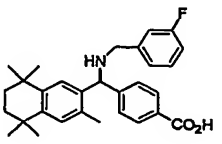
4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-methyl-2-naphthalenyl)(benzamido) methyl]benzoic acid (Compound 162)



To a solution of methyl 4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-methyl-2-naphthalenyl) (benzamido)methyl]benzoate (8 mg, 0.017 mmol) in 1 mL of THF was added 0.5 mL of 0.5M aqueous LiOH solution. The mixture was stirred for 3 days at room temp. before treatment with 1M aqueous HCl solution and extraction with EtOAc. The organic layer was dried and concentrated to leave 6 mg (75%) of 4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-methyl-2-naphthalenyl)(benzamido)methyl]benzoic acid (compound 162) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.01 (d, J = 8.5 Hz, 2H), 7.80 (d, J = 8.5 Hz, 2H), 7.47 (tt, J = 1.2, 7.3 Hz, 1H), 7.40 (d, J = 7.9 Hz, 1H) 7.39 (d, J = 7.0 Hz, 1H), 7.35 (d, J = 8.2 Hz, 2H), 7.07 (s, 1H), 6.87 (s, 1H), 6.86 (d, J = 7.9, 1H), 6.56 (d, J = 7.6, 1H), 2.23 (s, 3H), 1.59 (m, 4H), 1.23 (s, 3H), 1.22 (s, 3H), 1.10 (s, 3H), 1.01 (s, 3H).

Example 63

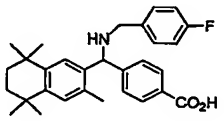
4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-methyl-2-naphthalenyl)(3-fluorobenzylamino) methyl]benzoic acid (Compound 163)



A suspension of methyl 4-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl) (hydroxymethyl] benzoate (106 mg, 0.29 mmol) in 2 mL CH_2Cl_2 was slowly added to 1.5 mL of conc. HCl. The mixture was stirred vigorously overnight, then diluted with 10 mL of CH_2Cl_2. The solution was washed with 10 mL of water and 10 mL of brine, dried and concentrated to leave 106 mg of methyl 4-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)(chloromethyl] benzoate as a pale yellow oil. To a solution of this chloride (100 mg, 0.26 mmol) and 3-fluorobenzylamine (0.10 mL, 0.88 mmol) in 1 mL of CH_3CN was added K_2CO_3 (75 mg, 0.54 mmol). The reaction mixture was stirred at room temp. for 18 h, then at reflux for 3 h before dilution with 15 mL of EtOAc. The mixture was washed with 10 mL of water and 10 mL of brine, dried and concentrated to leave 136 mg of crude methyl-4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-methyl-2-naphthalenyl)(3-fluorobenzylamino) methyl]benzoate as a yellow oil. This material was dissolved in 1 mL of THF and 1 mL of methanol. To this solution was added LiOH monohydrate (45 mg, 1.1 mmol) and 0.5 mL of water, and the resulting mixture was stirred overnight at ROOM TEMP.. The mixture was diluted with 5 mL of 0.1 M aqueous HCl solution and extracted with 15 mL of EtOAc. The organic layer was dried and concentrated to leave an oily residue that was purified by reverse-phase HPLC (2" C18 column, 80 mL/min 80:20:0.1 methanol/water/trifluoroacetic acid) to afford 43 mg (34% from alcohol x) of 4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-methyl-2-naphthalenyl)(3-fluorobenzylamino)methyl] benzoic acid (compound 163) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.00 (s, 1H), 7.74 (d, J = 8.3 Hz, 2H), 7.38 (d, J = 8.3 Hz, 2H), 7.36 (m, J = 7.3 Hz, 1H), 7.09 (m, J = 7.3 Hz, 2H), 7.07 (s, 1H), 6.99 (d, J = 9.3 Hz, 1H), 5.19 (s, 1H), 4.21 (d, J = 12.2 Hz, 1H), 3.95 (d, J = 13.2 Hz, 1H), 2.01 (s, 3H), 1.73 (m, 4H), 1.45 (s, 3H), 1.38 (s, 3H), 1.30 (s, 3H), 1.24 (s, 3H).

Example 64

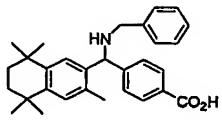
4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-methyl-2-naphthalenyl)(4-fluorobenzylamino) methyl]benzoic acid (Compound 164)



Compound 164 was synthesized from methyl 4-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)(hydroxymethyl] benzoate according to the procedure described in Example 63 using 4-fluorobenzylamine. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.05 (s, 1H), 7.69 (d, J = 8.3 Hz, 2H), 7.35 (d, J = 8.3 Hz, 2H), 7.30 (dd, J = 8, 8 Hz, 2H), 7.11 (dd, J = 8.3, 2H), 7.08 (s, 1H), 5.15 (s, 1H), 4.28 (d, J = 13 Hz, 1H), 3.95 (d, J = 13 Hz, 1H), 2.03 (s, 3H), 1.74 (m, 4H), 1.46 (s, 3H), 1.40 (s, 3H), 1.31 (s, 3H), 1.24 (s, 3H).

Example 65

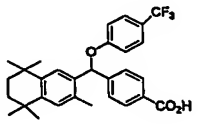
4-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)(benzylamino)methyl]benzoic acid (Compound 165)



Compound 165 was synthesized from methyl 4-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)(hydroxymethyl] benzoate according to the procedure described in Example 63 using benzylamine. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.09 (s, 2H), 7.88 (s, 1H), 7.75 (d, J = 8.0 Hz, 2H), 7.51 (d, J = 8.0 Hz, 1H), 7.29-7.07 (m, 5H), 4.89 (s, 2H), 1.76 (broad s, 4H), 1.37 (s, 6H), 1.25 (s, 6H).

Example 66

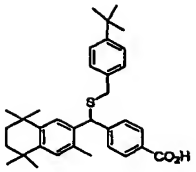
4-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)(4-trifluoromethylphenoxy) methyl]benzoic acid (Compound 166)



To a suspension of methyl 4-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl) (chloromethyl] benzoate (150 mg, 0.39 mmol) in 3 mL DMF was added 64 mg (0.40 mmol) and 100 mg (0.722 mmol) of K_2CO_3. The mixture was stirred overnight at room temperature, then diluted with 10 mL of water and extracted with EtOAc. The solution was washed with 3 mL of water (3 times) and 3 ml of brine, then dried over $MgSO_4$. After filtration, the solvents were removed under reduced pressure and the crude oil was directly diluted into 6 ml of a 1/1/1 mixture of THF/MeOH/2N aqueous LiOH. After complexion and work-up the crude acid was recrystallized from hexanes to afford 149 mg (0.3 mmol, yield: 85 %) of 4-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)(4-trifluoromethylphenoxy) methyl]benzoic acid (compound 166) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.10 (d, J = 7.9 Hz, 2H), 7.48 (d, J = 8.5 Hz, 4H), 7.11 (s, 1H), 7.07 (s, 1H), 6.97 (d, J = 8.5 Hz, 2H), 6.40 (s, 1H), 2.28 (s, 3H), 1.64 (m, 4H), 1.27 (s, 3H), 1.26 (s, 3H), 1.12 (s, 6H).

Example 67

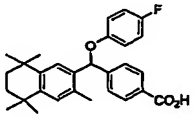
4-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)(4-tert-butylbenzylthio)methyl] benzoic acid (Compound 167)



Compound 167 was synthesized from methyl 4-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl) (chloromethyl] benzoate according to the procedure described in Example 66 using 4-tert-butylbenzylmercaptan as alkylating reagent. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.02 (d, J = 8.5 Hz, 2H), 7.47 (s, 1H), 7.45 (d, J = 8.2 Hz, 2H), 7.31 (d, J = 8.2 Hz, 2H), 7.10 (d, J = 8.0, 2H), 6.99 (s, 1H), 5.06 (s, 1H), 3.56 (q, J = 13.1Hz, 2H), 2.01 (s, 3H), 1.65 (m, 4H), 1.32 (s, 9H), 1.29 (s, 3H), 1.26 (s, 3H), 1.23 (s, 3H), 1.19 (s, 3H).

Example 68

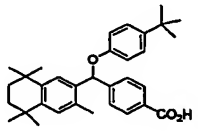
4-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)(4-fluorophenyloxy)methyl] benzoic acid (Compound 168)



Compound 168 was synthesized from methyl 4-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl) (chloromethyl] benzoate according to the procedure described in Example 66 using 4-fluorophenol as alkylating reagent. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.08 (d, J = 7.9 Hz, 2H), 7.48 (d, J = 7.9 Hz, 2H), 7.10 (s, 2H), 6.90 (dd, J = 9.2, 8.2 Hz, 2H), 6.84 (m, 2H), 6.26 (s, 1H), 2.27 (s, 3H), 1.64 (m, 4H), 1.26 (s, 3H), 1.25 (s, 3H), 1.13 (s, 3H), 1.12 (s, 3H).

Example 69

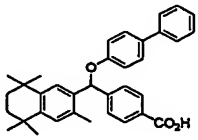
4-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)(4-tert-butylphenyloxy) methyl] benzoic acid (Compound 169)



Compound 169 was synthesized from methyl 4-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl) (chloromethyl)] benzoate according to the procedure described in Example 66 using 4-tert-butylphenol as alkylating reagent. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.09 (d, J = 7.6 Hz, 2H), 7.50 (d, J = 7.9 Hz, 2H), 7.22 (d, J = 8.9 Hz, 2H), 7.10 (s, 1H), 7.04 (s, 1H), 6.84 (d, J = 8.9 Hz, 2H), 6.32 (s, 1H), 2.28 (s, 3H), 1.63 (m, 4H), 1.26 (s, 15H), 1.13 (s, 3H), 1.10 (s, 3H).

Example 70

4-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)(4-phenylphenyloxy) methyl]benzoic acid (Compound 170)

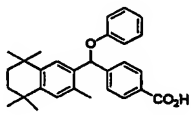


Compound 170 was synthesized from methyl 4-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl) (chloromethyl)] benzoate according to the procedure described in Example 66 using 4-phenylphenol as alkylating reagent. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.10 (d, J = 7.9 Hz, 2H), 7.52 (dd, J = 9.5, 8.2 Hz, 2H), 7.45 (d, J = 8.9 Hz, 2H), 7.39 (dd, J = 8.5, 8.5 Hz, 1H), 7.29 (d, J = 8.5 Hz, 2H), 7.11 (s, 1H), 7.09 (s,

1H), 6.98 (d, J = 8.9 Hz, 2H), 6.40 (s, 1H), 2.31 (s, 3H), 1.64 (m, 4H), 1.27 (s, 3H), 1.26 (s, 3H), 1.15 (s, 3H), 1.12 (s, 3H).

Example 71

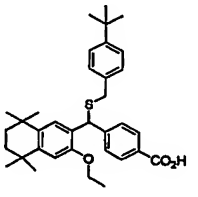
4-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)(4-phenoxy)methyl]benzoic acid (Compound 171)



Compound 171 was synthesized from methyl 4-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl) (chloromethyl)] benzoate according to the procedure described in Example 66 using phenol as alkylating reagent. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.09 (d, J = 8.2 Hz, 2H), 7.50 (d, J = 8.2 Hz, 2H), 7.10 (s, 1H), 7.08 (s, 1H), 6.919 (m, 3H2.29 (s, 3H), 1.63 (m, 4H), 1.27 (s, 3H), 1.26 (s, 3H), 1.13 (s, 3H), 1.11 (s, 3H).

Example 72

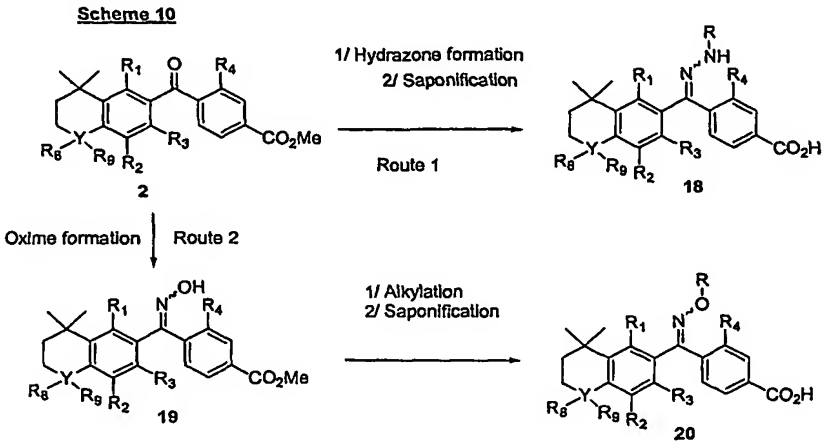
4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethoxy-2-naphthalenyl)(4-tert-butylbenzylthio) methyl]benzoic acid (Compound 172)



Compound 172 was synthesized from methyl 4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethoxy-2-naphthalenyl) (chloromethyl)] benzoate according to the procedure described

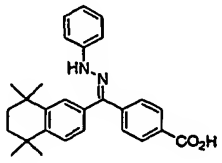
in Example 66 using 4-tert-butylbenzylmercaptan as alkylating reagent. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.99 (d, J = 8.2 Hz, 2H), 7.52 (s, 1H), 7.50 (d, J = 8.5 Hz, 2H), 7.29 (d, J = 8.2 Hz, 2H), 6.66 (s, 1H), 5.46 (s, 1H), 3.89 (m, 2H), 3.56 (ABq, JAB = 13.1 Hz, 2H), 1.65 (m, 4H), 1.31 (s, 9H), 1.29 (s, 3H), 1.26 (t, J = 7.0 Hz, 3H), 1.25 (s, 3H), 1.22 (s, 6H).

Compounds of formula 17 and 19 may be synthesized using the following procedures:



Example 73

4-[(phenylhydrazino)(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)] benzoic acid (Compound 173)

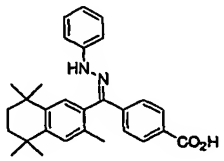


To a mixture of 4.7 g (13.99 mmol) of 4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)] benzoic acid and 4.5 g (41.96 mmol) of phenyl hydrazine in 15 ml of EtOH, was added 1 ml of AcOH. The mixture was refluxed overnight and after cooling

at room temperature, the solvents were removed under reduced pressure. The yellow crude product was recrystallized twice from Et2O and EtOAc to afford 2.0 g (4.69 mmol, yield: 34 %) of 4-[(phenylhydrazino)(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)] benzoic acid as a bright yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.05 (s, J = 8.5 Hz, 2H), 7.85 (s, 1H), 7.71 (d, J = 10.0 Hz, 2H), 7.51 (d, J = 8.0 Hz, 1H), 7.29 (d, J = 7.0 Hz, 1H), 7.12 (d, J = 7.5, 2H), 7.07 (dd, J = 8.0, 2.0 Hz, 1H), 6.89 (t, J = 7.5 Hz, 1H), 1.76 (broad s, 4H), 1.38 (s, 6H), 1.29 (s, 6H).

Example 74

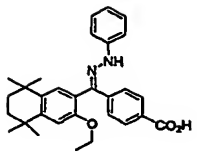
4-[(phenylhydrazino)(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)] benzoic acid (Compound 174)



Compound 174 was synthesized from methyl 4-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethoxy-2-naphthalenyl)benzoyl benzoate according to the procedure described in Example 73 using phenylhydrazine. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.05 (s, J = 8.5 Hz, 2H), 7.85 (s, 1H), 7.71 (d, J = 10.0 Hz, 2H), 7.51 (d, J = 8.0 Hz, 1H), 7.29 (d, J = 7.0 Hz, 1H), 7.12 (d, J = 7.5, 2H), 7.07 (dd, J = 8.0, 2.0 Hz, 1H), 6.89 (t, J = 7.5 Hz, 1H), 1.76 (broad s, 4H), 1.38 (s, 6H), 1.29 (s, 6H).

Example 75

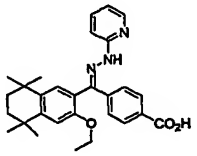
4-[(phenylhydrazonyl)(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethyloxy-2-naphthalenyl)] benzoyl benzoic acid (Compound 175)



Compound 175 was synthesized from methyl 4-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethoxy-2-naphthalenyl)benzoyl benzoate according to the procedure described in Example 73 using phenylhydrazine. ^{1}H NMR (500 MHz, DMSO-d_6) 8.05(d, J=8.3 Hz, 2H), 7.78 (s, 1H), 7.72 (d, J=8.3 Hz, 2H), 7.31-7.27 (m, 4H), 7.17-7.14 (m, 2H), 7.11 (s, 1H), 6.99 (s, 1H), 6.89 (t, J=7.3 Hz, 1H), 4.00(q, J=6.8 Hz, 2H), 1.80-1.70 (m, 4H), 1.60 (br. s, 1H), 1.39 (s, 6H), 1.25(s, 6H), 1.15 (t, J=6.8 Hz, 3H).

Example 76

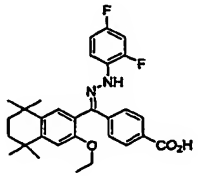
4-[(Pyridine-2-hydrazonyl)(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethyloxy-2-naphthalenyl)]benzoyl benzoic acid (Compound 176)



Compound 176 was synthesized from methyl 4-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethoxy-2-naphthalenyl)benzoyl benzoate according to the procedure described in Example 73 using 2-pyridylhydrazine. ^{1}H NMR (500 MHz, DMSO-d_6) 12.95 (br. s, 1H), 8.20 (s, 1H), 8.07(m, 1H), 7.94 (d, J=8.7 Hz, 2H), 7.74 (m, 1H), 7.62 (d, J=8.7 Hz, 2H), 7.45 (d, J=8.3 Hz, 1H), 7.15 (s, 1H), 7.13 (s, 1H), 6.86 (m, 1H), 4.06(q, J=6.8 Hz, 2H), 1.70-1.60 (m, 4H), 1.36 (s, 6H), 1.21(s, 6H), 1.03 (t, J=6.8 Hz, 3H).

Example 77

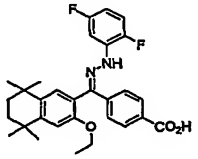
4-[(2,4-Difluorophenylhydrazonyl)(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethyloxy-2-naphthalenyl)] benzoyl benzoic acid (Compound 177)



Compound 177 was synthesized from methyl 4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethoxy-2-naphthalenyl)benzoyl benzoate according to the procedure described in Example 73 using 2,4-difluorophenylhydrazine. ^{1}H NMR (500 MHz, DMSO-d_6) 12.92 (br. s, 1H), 7.93(d, *J*=8.8 Hz, 2H), 7.89 (d, *J*=2.0 Hz, 1H), 7.70-7.64 (m, 1H), 7.61 (d, *J*=8.8 Hz, 2H), 7.28-7.22 (m, 1H), 7.18 (s, 1H), 7.15 (s, 1H), 7.11-7.06 (m, 1H), 4.05(q, *J*=6.8 Hz, 2H), 1.72-1.64 (m, 4H), 1.35 (s, 6H), 1.20(s, 6H), 1.02 (t, *J*=6.8 Hz, 3H).

Example 78

4-[(2,5-Difluorophenylhydrazonyl)(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethyloxy-2-naphthalenyl)] benzoyl benzoic acid (Compound 178)

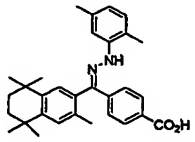


Compound 178 was synthesized from methyl 4-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethoxy-2-naphthalenyl)benzoyl benzoate according to the procedure described in Example 73 using 2,5-difluorophenylhydrazine. ^{1}H NMR (500 MHz, DMSO-d_6) 12.93 (br. s, 1H), 8.02 (s, 1H), 7.94 (d, *J*=8.8 Hz, 2H), 7.65 (d, *J*=8.8 Hz, 2H), 7.47-7.42 (m,

1H), 7.24-7.18 (m, 1H), 7.19 (s, 1H), 7.16 (s, 1H), 6.68-6.62 (m, 1H), 4.05(q, *J*=6.8 Hz, 2H), 1.72-1.64 (m, 4H), 1.35 (s, 6H), 1.20(s, 6H), 1.02 (t, *J*=6.8 Hz, 3H).

Example 79

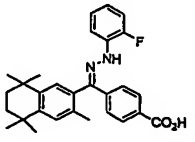
4-[(2,5-Dimethylphenylhydrazonyl)(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)] benzoyl benzoic acid (Compound 179)



Compound 179 was synthesized from methyl 4-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)benzoyl benzoate according to the procedure described in Example 73 using 2,5-dimethylphenylhydrazine. ^{1}H NMR (500 MHz, DMSO-d_6) 12.95 (br. s, 1H), 8.00 (s, 1H), 7.93 (d, *J*=8.8 Hz, 2H), 7.62 (d, *J*=8.8 Hz, 2H), 7.43-7.46 (m, 1H), 7.20-7.14 (m, 1H), 7.12 (s, 1H), 7.11 (s, 1H), 6.65-6.60 (m, 1H), 4.03 (q, *J*=6.9 Hz, 2H), 2.10 (s, 3H), 2.05 (s, 3H), 1.70-1.65 (m, 4H), 1.34 (s, 6H), 1.20 (s, 6H), 1.01 (t, *J*=6.9 Hz, 3H).

Example 80

4-[(2-fluorophenylhydrazonyl)(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)] benzoyl benzoic acid (Compound 180)

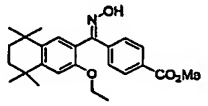


Compound 180 was synthesized from methyl 4-[(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)benzoyl benzoate according to the procedure described in

Example 73 using 2-fluorophenylhydrazine. ^{1}H NMR (500 MHz, DMSO-d_6) 12.90 (br. s, 1H), 8.02 (s, 1H), 7.94 (d, J=8.8 Hz, 2H), 7.65 (d, J=8.8 Hz, 2H), 7.47-7.42 (m, 1H), 7.24-7.18 (m, 1H), 7.19 (s, 1H), 7.16 (s, 1H), 6.68-6.62 (m, 1H), 4.05(q, J=6.8 Hz, 2H), 1.72-1.64 (m, 4H), 1.35 (s, 6H), 1.20(s, 6H), 1.02 (t, J=6.8 Hz, 3H).

Example 81

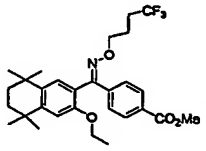
Methyl-4-[(oxyimino)(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethoxy-2-naphthalenyl)] benzoate (Compound 181)



To a solution of Methyl-4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethoxy-2-naphthalenyl)] benzoate (1.61 g, 4.22 mmol) in Ethanol (14 mL), was added pyridine (0.52 mL, 1.5 eq.), followed by hydroxylamine hydrochloride (0.587 g, 8.45 mmol). The solution was heated to reflux and stirred overnight. The reaction mixture was allowed to cool to room temperature, poured onto water (50 mL), and extracted with EtOAc (2 x 50 mL). The organic layers were combined, washed with brine (50 mL), and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the compound purified by flash chromatography (silica gel, 15% EtOAc/Hexanes) to give 1.24 g (72%) of the desired oxime (example 81) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.98 (d, J = 8.2 Hz, 2H), 7.57 (d, J = 8.2 Hz, 2H), 7.12 (s, 1H), 6.88 (s, 1H), 3.94 (dd, J = 13.7, 7.0 Hz, 2H), 3.92 (s, 3H), 1.70 (m, 4H), 1.33 (s, 6H), 1.24 (s, 6H), 1.11 (t, J = 7.0 Hz, 3H).

Example 82

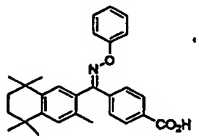
Methyl-4-[(4,4,4-trifluorobutoxyimino)(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethyloxy-2-naphthalenyl)] benzoate (Compound 182)



In a round bottom flask equipped with a magnetic stir bar, methyl-4-[(oxyimino)(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethoxy-2-naphthalenyl)] benzoate (1.24 g, 3.02 mmol) was dissolved in 14 mL dry ethanol and cooled to 0°C. Sodium hydride (60% in mineral oil, 0.138 g, 3.43 mmol) was added in one portion and the mixture was allowed to stir for 30 min. Via syringe, 1-iodo-4,4,4-trifluorobutane (1.30 g, 5.44 mmol) was added dropwise, and the reaction was allowed to warm to room temperature overnight. The reaction was poured onto water (50 mL), and extracted with EtOAc (2 x 50 mL). The organic layers were combined, washed with brine (50 mL), and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the compound purified by flash chromatography (silica gel, 25% EtOAc/Hexanes) to yield 1.09 g (70%) of methyl-4-[(4,4,4-trifluorobutoxyimino)(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethyloxy-2-naphthalenyl)] benzoate as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.96 (d, J = 8.7 Hz, 2H), 7.55 (d, J = 8.4 Hz, 2H), 7.05 (s, 1H), 6.83 (s, 1H), 4.25 (t, J = 6.0 Hz, 2H), 3.91 (s, 3H), 3.88 (dd, J = 13.9, 6.9 Hz, 2H), 2.15 (m, 2H), 1.96 (m, 2H), 1.70 (m, 4H), 1.32 (s, 6H), 1.23 (s, 6H), 1.06 (t, J = 6.8 Hz, 3H).

Example 83

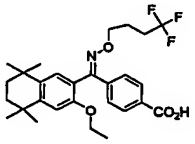
4-[(phenylimino)(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)] benzoyl benzoic acid (Compound 183)



Compound 183 was synthesized from methyl 4-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl)benzoyl benzoate according to the procedure described in Example 81 using *O*-phenylhydroxylamine hydrochloride. ^{1}H NMR (500 MHz, DMSO-d_6) 9.31 (br. s, 1H), 8.11 (d, J = 6.7 Hz, 2H), 7.73 (d, J= 6.7 Hz, 2H), 7.33 (m, 1H), 7.28 (m, 2H), 7.22 (m, 2H), 7.07 (m, 2H), 2.11 (s, 3H), 1.72 (s, 4H), 1.35 (s, 6H), 1.25 (s, 6H).

Example 84

4-[(1,1,1-trifluorobutoxyimino)(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethyloxy-2-naphthalenyl)] benzoic acid (Compound 184)

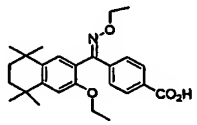


To a round bottom flask equipped with a magnetic stir bar was added 1.09 g of methyl-4-[(1,1,1-trifluorobutoxyimino)(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethyloxy-2-naphthalenyl)] benzoate (2.10 mmol) followed by 10 mL THF, 5 mL water, 3 mL MeOH, and lithium hydroxide monohydrate (0.880 g, 20.97 mmol). The mixture was stirred overnight at room temperature. The reaction was poured onto water (50 mL), and

extracted with EtOAc (2 x 50 mL). The organic layers were combined, washed with brine (50 mL), and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the compound purified by flash chromatography (silica gel, 50% EtOAc/Hexanes) to yield 0.354 g (35%) of 4-[(1,1,1-trifluorobutoxyimino)(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethyloxy-2-naphthalenyl)] benzoic acid as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.03 (d, J = 8.4 Hz, 2H), 7.58 (d, J = 8.5 Hz, 2H), 7.06 (s, 1H), 6.84 (s, 1H), 4.26 (t, J = 6.0 Hz, 2H), 3.89 (dd, J = 14.0, 6.9 Hz, 2H), 2.16 (m, 2H), 1.96 (m, 2H), 1.70 (m, 4H), 1.32 (s, 6H), 1.23 (s, 6H), 1.06 (t, J = 7.1 Hz, 3H).

Example 85

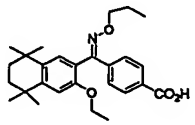
4-[(ethoxyimino)(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethyloxy-2-naphthalenyl)]benzoic acid (Compound 185)



Compound 185 was synthesized from methyl-4-[(oxyimino)(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethoxy-2-naphthalenyl)] benzoate according to the procedure described in Example 76 using ethyl iodide as alkylating agent. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.00 (d, J = 8.6 Hz, 2H), 7.59 (d, J = 8.4 Hz, 2H), 7.14 (s, 1H), 6.83 (s, 1H), 4.27 (dd, J = 14.1, 7.2 Hz, 2H), 3.88 (dd, J = 13.8, 6.9 Hz, 2H), 1.69 (m, 4H), 1.31 (m, 9H), 1.23 (s, 6H), 1.05 (t, J = 7.0 Hz, 3H).

Example 86

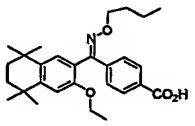
4-[(propoxyimino)(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethyloxy -2-naphthalenyl)] benzoic acid (Compound 186)



Compound 186 was synthesized from methyl-4-[(oxyimino)(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethoxy-2-naphthalenyl)] benzoate according to the procedure described in Example 84 using 1-iodopropane as alkylating agent ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.01 (d, J = 8.5 Hz, 2H), 7.58 (d, J = 8.5 Hz, 2H), 7.14 (s, 1H), 6.83 (s, 1H), 4.17 (dd, J = 6.7, 6.7 Hz, 2H), 3.87 (dd, J = 14.0, 7.0 Hz, 2H), 1.72 (m, 2H), 1.69 (m, 4H), 1.31 (s, 6H), 1.24 (s, 6H), 1.04 (t, J = 7.0 Hz, 3H), 0.94 (t, J = 7.3 Hz, 3H).

Example 87

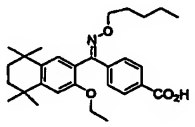
4-[(butoxyimino)(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethyloxy-2-naphthalenyl)]benzoic acid (Compound 187)



Compound 187 was synthesized from methyl-4-[(oxyimino)(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethoxy-2-naphthalenyl)] benzoate according to the procedure described in Example 84 using butyl iodide as alkylating agent. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.00 (d, J = 8.2 Hz, 2H), 7.58 (d, J = 8.2 Hz, 2H), 7.13 (s, 1H), 6.82 (s, 1H), 4.22 (dd, J = 6.7, 6.7 Hz, 2H), 3.87 (dd, J = 13.7, 7.0 Hz, 2H), 1.68 (m, 4H), 1.31 (s, 6H), 1.24 (s, 6H), 1.04 (t, J = 7.0 Hz, 3H), 0.92 (t, J = 7.3 Hz, 3H).

Example 88

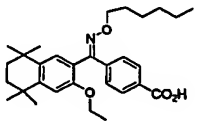
4-[(pentoxyimino)(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethyloxy -2-naphthalenyl)] benzoic acid (Compound 188)



Compound 188 was synthesized from methyl-4-[(oxyimino)(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethoxy-2-naphthalenyl)] benzoate according to the procedure described in Example 84 using pentyl iodide as alkylating agent. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.00 (d, J = 8.5 Hz, 2H), 7.57 (d, J = 8.5 Hz, 2H), 7.13 (s, 1H), 6.82 (s, 1H), 4.20 (dd, J = 6.9, 6.9 Hz, 2H), 3.86 (dd, J = 14.0, 6.9 Hz, 2H), 1.69 (m, 4H), 1.33-1.25 (m, 6H), 1.31 (s, 6H), 1.23 (s, 6H), 1.03 (t, J = 6.9 Hz, 3H), 0.90 (m, 3H).

Example 89

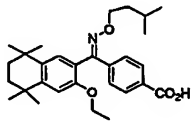
4-[(hexyloxyimino)(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethyloxy -2-naphthalenyl)] benzoic acid (Compound 189)



Compound 189 was synthesized from methyl-4-[(oxyimino)(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethoxy-2-naphthalenyl)] benzoate according to the procedure described in Example 84 using 1-iodohexane as alkylating agent. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.00 (d, J = 8.5 Hz, 2H), 7.57 (d, J = 8.5 Hz, 2H), 7.14 (s, 1H), 6.82 (s, 1H), 4.20 (dd, J = 6.7, 6.7 Hz, 2H), 3.86 (dd, J = 13.9, 6.9 Hz), 1.69 (m, 4H), 1.31 (s, 3H), 1.26 (m, 7H), 1.23 (s, 3H), 1.03 (s, 3H), 0.87 (m, 4H).

Example 90

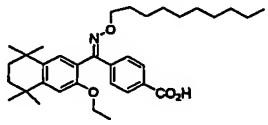
4-[(3-methyl-butoxyimino)(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethyloxy -2-naphthalenyl)]benzoic acid (Compound 190)



Compound 190 was synthesized from methyl-4-[(oxyimino)(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethoxy-2-naphthalenyl)] benzoate according to the procedure described in Example 84 using 1-iodo-3-methylbutane as alkylating agent. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.01 (d, J = 8.5 Hz, 2H), 7.58 (d, J = 8.5 Hz, 2H), 7.12 (s, 1H), 6.82 (s, 1H), 4.24 (dd, J = 6.9, 6.9 Hz, 2H), 3.86 (dd, J = 14.0, 6.9 Hz, 2H), 1.69 (m, 4H), 1.58 (m, 3H), 1.31 (s, 6H), 1.23 (s, 6H), 1.03 (t, J = 6.9 Hz, 3H), 0.91 (s, 3H), 0.89 (s, 3H).

Example 91

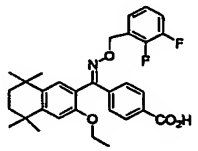
4-[(decyloxyimino)(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethyloxy -2-naphthalenyl)] benzoic acid (Compound 191)



Compound 191 was synthesized from methyl-4-[(oxyimino)(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethoxy-2-naphthalenyl)] benzoate according to the procedure described in Example 84 using 1-iododecane as alkylating agent. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.02 (d, J = 8.5 Hz, 2H), 7.58 (d, J = 8.5 Hz, 2H), 7.14 (s, 1H), 6.82 (s, 1H), 4.20 (dd, J = 7.0, 7.0 Hz, 2H), 3.87 (dd, J = 14.0, 7.0 Hz, 2H), 1.69 (m, 4H), 1.28 (m, 28H), 1.04 (t, J = 7.0 Hz, 3H), 0.88 (t, J = 7.0 Hz, 3H).

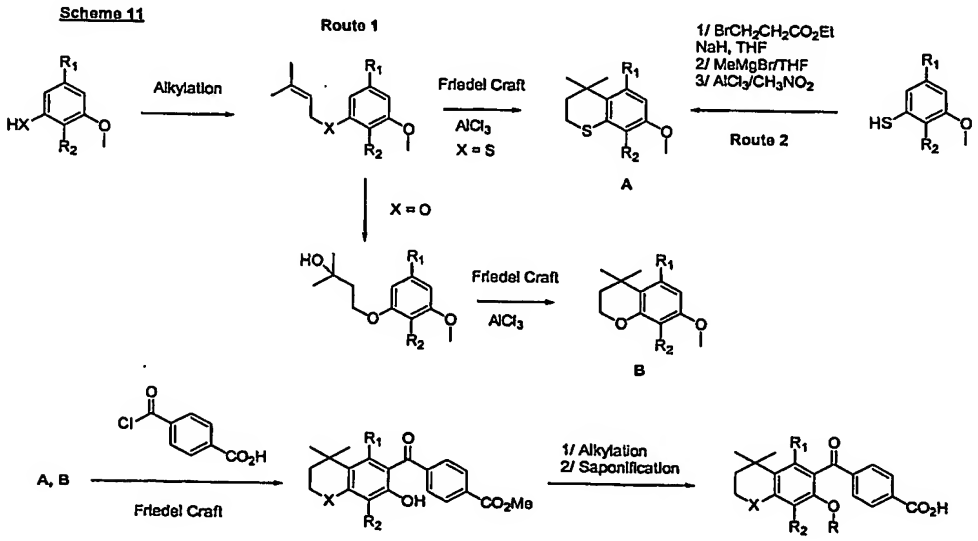
Example 92

4-[(2,3-difluorobenzyloxyimino)(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethyloxy -2-naphthalenyl)] benzoic acid (Compound 192)



Compound 192 was synthesized from methyl-4-[(oxyimino)(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethoxy-2-naphthalenyl)] benzoate according to the procedure described in Example 84 using 2,3-difluorobenzyl bromide as alkylating agent. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.02 (d, J = 8.3 Hz, 2H), 7.58 (d, J = 8.3 Hz, 2H), 7.20 (m, 1H), 7.11 (m, 1H), 7.06 (s, 1H), 6.85 (s, 1H), 5.35 (s, 2H), 3.89 (dd, J = 13.7, 6.8 Hz, 2H), 1.70 (m, 4H), 1.33 (s, 6H), 1.23 (s, 6H), 1.05 (t, J = 6.8 Hz, 3H).

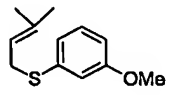
Compounds possessing a heteroatom at the Y position may be synthesized using the following scheme:



Example 93

(Route 1)

3-[(3-methyl)but-3-ene]thio anisole (Compound 193)

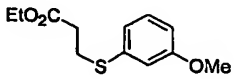


To a suspension of 1.73 g (36.1 mmol) of NaH in 20 ml of dry THF was added dropwise 4.23 g (3.75 ml, 30.1 mmol) of 3-methoxy thiophenol diluted in 50ml of dry THF at 0° C. The mixture was stirred 30 minutes at this temperature then 5g (3.9 ml, 33.5 mmol) of 1-bromo-3-methyl-3-butene diluted in 5 ml of dry THF was added slowly. The resulting solution was warmed to room temperature and stirred 3 hours. Cold water (100 ml) was carefully added and the mixture was extracted twice with EtOAc. The organic layers were collected, washed with water (2 times 10 ml) and brine (10 ml), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The resulting oil was purified over silica gel column chromatography (eluent: 90/10: hexane/EtOAc to afford 5 g (24.0 mmol, yield: 80 %) of 3-[(3-methyl)but-3-ene]thio anisole as a clear oil. ^1H NMR (500 MHz, $CDCl_3$) δ: 7.18 (t, J = 8.2 Hz, 1H), 6.92 (d, J = 8.2 Hz, 1H), 6.91 (d, J = 0.5 Hz, 1H), 6.68 (dd, J = 8.2, 0.5 Hz, 1H), 5.30 (m, 1H), 3.79 (s, 3H), 3.78 (d, J = 3.4 Hz, 2H), 1.72 (s, 3H), 1.63 (s, 3H).

Example 94

(Route 2)

Ethyl-(3-methoxybenzyl)thiopropionate (Compound 194)

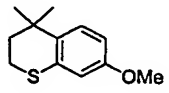


To a suspension of 858 m g (12 mmol) of NaH in 10 ml of dry THF was added dropwise 1.4 g (1.2 ml, 10.0 mmol) of 3-methoxy thiophenol and 2.17 g (1.5 ml, 10.0 mmol) of ethyl-3-bromopropionate diluted in 10ml of dry THF at 0° C. The mixture was warmed to room temperature and stirred 3 hours at 50° C. After cooling at room temperature, cold water (100 ml) was carefully added and the mixture was extracted twice with EtOAc. The organic layers were collected, washed with water (2 times 10 ml) and brine (10 ml), dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The resulting oil was purified over silica gel column chromatography (eluent: 90/10: hexane/EtOAc to afford 2.36 g (9.8 mmol, yield: 98 %) of 3-[(3-methyl)but-3-ene]thio anisole as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.21 (t, J = 7.9 Hz, 1H), 6.93 (d, J = 7.9 Hz, 1H), 6.90 (d, J = 1.5 Hz, 1H), 6.65 (dd, J = 7.9, 15 Hz, 1H), 4.15 (dd, J = 14.3, 7.2 Hz, 2H), 3.81 (s, 3H), 3.17 (t, J = 7.6 Hz, 2H), 2.64 (t, J = 7.6 Hz, 2H), 1.26 (t, J = 7.2 Hz, 3H).

Example 95

(Route 1)

2,3-dihydro-4,4-dimethyl-7-methoxybenzothiopyrane (Compound 195)

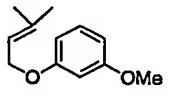


To a solution of 2 g (9.6 mmol) of substrate diluted in 25 ml of benzene was added 1.9 g (1.1 ml, 19.4 mmol) of H_3PO_4 and the mixture was refluxed for 2 hours. After cooling at room temperature, 4.1 g (14.4 mmol) of P_2O_5 was added and the solution is refluxed for an extra 2 hours. After cooling at room temperature, ice (100 g) was added and the mixture was extracted with EtOAc. The organic layers were collected and washed with water and brine, then dried over $MgSO_4$. After filtration and concentration, the resulting oil was purified over silica gel column chromatography (eluent: 95/5 hexane/EtOAc) to afford 1.5 g (7.2 mmol, yield: 75 %) of desired product as a pale brown oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.26 (d, J = 8.8 Hz, 1H), 6.61 (d, J = 8.8 Hz, 1H), 6.59 (s, 1H), 3.75 (s, 3H), 3.02 (t, J = 6.1 Hz, 2H), 1.95 (d, J = 6.1 Hz, 2H), 1.30 (s, 6H).

Example 96

(Route 1)

3-[(3-methyl)but-3-eneoxy] anisole (Compound 196)

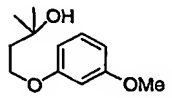


To a suspension of 3.5 g (72.2 mmol) of NaH in 70 ml of THF was added dropwise 7.5 g (diluted in 3 ml of dry THF) at 0° C. After 10 minutes, 10 gm (67.1 mmol, 7.9 ml,

diluted in 10 ml of dry THF) was added slowly and the mixture was stirred at room temperature overnight. After work-up, the crude ether was purified over SiO_2 column chromatography to afford 9.27 g (48.2 mmol, 80 %) of 3-[(3-methyl)but-3-eneoxy] anisole as pale brown oil. ^1H NMR (500 MHz, $CDCl_3$) δ: 7.19 (t, J = 8.1 Hz, 1H), 6.90 (dd, J = 8.1, 1.6 Hz, 1H), 6.80 (d, J = 1.5 Hz, 1H), 5.45 (m, 1H), 4.50 (d, J = 7.02 Hz, 2H), 3.79 (s, 3H), 1.80 (s, 3H), 1.75 (s, 3H).

Example 97

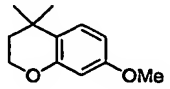
3-[(3-methyl-3-hydroxy)butanoxy]anisole (Compound 197)



To a suspension of 3.0 g (15.6 mmol) of 3-[(3-methyl)but-3-eneoxy] anisole in 40 ml of a 1/1 mixture of THF/water was added 4.97 g (15.6 mmol) of $Hg(OAc)_2$ at 0° C. After 1 hour, 10 ml of a 2N aqueous NaOH solution was added followed by 1.2 g (31.2 mmol) of $NaBH_4$. The ash-colored solution was then filtrated over a celite plug, extracted with EtOAc, dried over $MgSO_4$, filtrated and concentrated. The crude alcohol was purified over SiO_2 plug to afford 1.65 g 7.61 mmol, 49 %) of 3-[(3-methyl-3-hydroxy)butanoxy] anisole as clear oil. ^1H NMR (500 MHz, $CDCl_3$) δ: 7.18 (t, J = 8.1 Hz, 1H), 6.91 (dd, J = 8.1, 1.5 Hz, 1H), 6.85 (d, J = 1.5 Hz, 1H), 4.17 (t, J = 6.4 Hz, 2H), 3.79 (s, 3H), 1.99 (t, J = 6.4 Hz, 2H), 1.59 (s, 6H).

Example 98

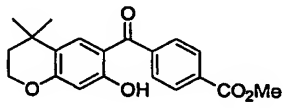
2,3-dihydro-4,4-dimethyl-7-methoxybenzopyran (Compound 198)



To a solution of 1.0 g (7.5 mmol) of $AlCl_3$ diluted in 10 ml of CH_3NO_2 was added dropwise 1.6 g (7.6 mmol) of 3-[(3-methyl-3-hydroxy)butanoxy] anisole diluted in 5 ml of CH_3NO_2 at 0° C. The mixture was warmed-up to room temperature and stirred for 2 hours, quenched with ice and extracted with CH_2Cl_2. The organic layers were dried over $MgSO_4$, filtrated and concentrated under reduced pressure. The crude product was purified over silica gel column chromatography to afford 850 mg (4.42 mmol, yield: 58 %) of the desired adduct as a pale brown oil. ^1H NMR (500 MHz, $CDCl_3$) δ: 7.26 (d, J = 8.8 Hz, 1H), 6.61 (d, J = 8.8 Hz, 1H), 6.59 (s, 1H), 3.75 (s, 3H), 3.02 (t, J = 6.1 Hz, 2H), 1.95 (d, J = 6.1 Hz, 2H), 1.30 (s, 6H).

Example 99

Methyl-6-[(2,3-dihydro-4,4-dimethyl-7-hydroxy-benzopyranyl)]benzoyl benzoate (Compound 199)

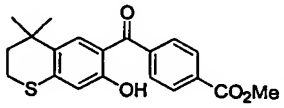


To a mixture of 850 mg (4.4 mmol) of substrate with 858 mg (4.6 mmol) of methyl-4-chlorocarbonyl benzoate in 15 ml of dry 1,2-dichloroethane was added 1.76 g (13.2 mmol) of $AlCl_3$ at room temperature. The reddish mixture was refluxed for 4 hours and poured into ice (50 g) after cooling down to room temperature. The yellowish mixture

was separated and the aqueous layer extracted twice with CH_2Cl_2. The organic layers were collected, dried over $MgSO_4$, filtrated and concentrated. The crude product was purified over silica gel column chromatography to afford 360 mg (0.1.06 mmol, yield: 24 %) of the desired adduct as a pasty yellow pasty oil. ^1H NMR (500 MHz, $CDCl_3$) δ: 12.0 (s, 1H), 8.18 (d, J = 7.9 Hz, 2H), 7.69 (d, J = 7.9 Hz, 2H), 7.39 (s, 1H), 6.43 (s, 1H), 4.28 (t, J = 5.5 Hz, 2H), 3.98 (s, 3H), 1.82 (t, J = 5.5 Hz, 2H), 1.21 (s, 6H).

Example 100

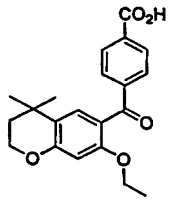
Methyl-6-[(2,3-dihydro-4,4-dimethyl-7-hydroxy-benzothiopyranyl)]benzoyl benzoate (Compound 200)



To a mixture of 700 mg (3.36 mmol) of substrate with 667 mg (3.36 mmol) of methyl-4-chlorocarbonyl benzoate in 15 ml of dry 1,2-dichloroethane was added 1.35 g (10.1 mmol) of $AlCl_3$ at room temperature. The reddish mixture was refluxed for 4 hours and poured into ice (50 g) after cooling down to room temperature. The yellowish mixture was separated and the aqueous layer extracted twice with CH_2Cl_2. The organic layers were collected, dried over $MgSO_4$, filtrated and concentrated. The crude product was purified over silica gel column chromatography to afford 60 mg (0.168 mmol, yield: 5 %) of the desired adduct (as well as 110 mg - 0.308 mmol, yield: 9 %- of the other adduct) as a yellow pasty oil. ^1H NMR (500 MHz, $CDCl_3$) δ: 11.8 (s, 1H), 8.22 (d, J = 7.8 Hz, 2H), 7.71 (d, J = 7.8 Hz, 2H), 7.45 (s, 1H), 6.81 (s, 1H), 3.98 (s, 3H), 3.02 (m, 2H), 1.92 (m, 2H), 1.20 (s, 6H).

Example 101

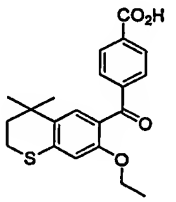
6-[(2,3-dihydro-4,4-dimethyl-7-ethoxy-benzopyranyl)]benzoyl benzoic acid (Compound 201)



Example 93 was synthesized from Methyl-6-[(2,3-dihydro-4,4-dimethyl-7-hydroxy-benzopyranyl)]benzoyl benzoate according to the procedure described in Example 3 using ethyl iodide as alkylating agent. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.14 (d, J = 8.2 Hz, 2H), 7.78 (d, J = 8.2 Hz, 2H), 7.56 (s, 1H), 6.33 (s, 1H), 4.27 (t, J = 5.5 Hz, 2H), 3.81 (dd, J = 13.7, 7.0 Hz, 2H), 1.86 (t, J = 5.2 Hz, 2H), 1.35 (s, 6H), 0.92 (t, J = 7.0 Hz, 3H).

Example 102

6-[(2,3-dihydro-4,4-dimethyl-7-ethoxy-benzothiopyranyl)]benzoyl benzoic acid (Compound 202)

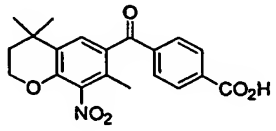


Example 102 was synthesized from Methyl-6-[(2,3-dihydro-4,4-dimethyl-7-hydroxy-benzothiopyranyl)]benzoyl benzoate according to the procedure described in Example 3 using ethyl iodide as alkylating agent. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.11 (d, J = 8.2

Hz, 2H), 7.80 (d, J = 8.2 Hz, 2H), 7.57 (s, 1H), 6.63 (s, 1H), 3.83 (dd, J = 14.0, 7.0 Hz, 2H), 3.08 (t, J = 6.1 Hz, 2H), 1.98 (m, 2H), 1.34 (s, 6H), 0.93 (t, J = 7.0 Hz, 3H).

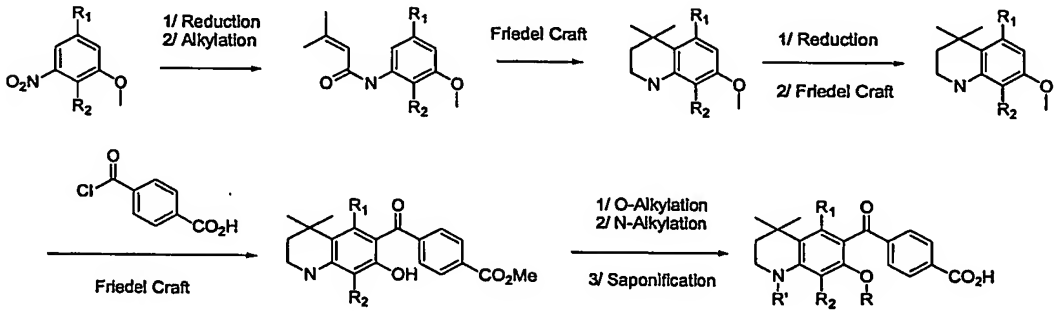
Example 103

6-[(2,3-dihydro-4,4,7-trimethyl-8-nitrobenzopyranyl)]benzoic acid (Compound 203)



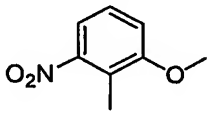
Example 103 was synthesized from 6-[(2,3-dihydro-4,4,7-trimethylbenzopyranyl)]benzoic acid according to the procedure described for the synthesis of compound 108.

Scheme 12



Example 104

2-methyl-3-nitro anisole (Compound 204)

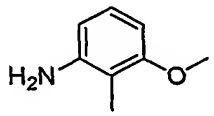


A solution of 3-nitro,2-methylphenol (5g, 33mmol), in a flame dried flask in dry DMF (160 mls) under nitrogen was cooled to 0C using an ice/water bath. To the cooled mix

was added sodium hydride (1.96g, 49mmol), and the reaction mix turned a blood red color and allowed to stir for 4hrs. The reaction was diluted down with hexanes and directly purified using a silica packed plug (Hexanes/EtoAc) resulting in a yellow solid which was the desired product (4.8g, 89%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (dd, J = 1.2, 8.2 Hz, 1H), 7.27 (m, 1H), 7.04 (d, J = 8.2 Hz, 1H), 3.89 (s, 3H), 2.36 (s, 3H).

Example 105

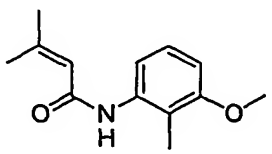
3-amino-2-methyl anisole (Compound 205)



To a solution of 3-nitro,2-methylmethoxybenzene (4.85g, 29mmol) in 100mls ethylacetate was added approximately 750mgs of Palladium/carbon. The reaction vessel atmosphere was evacuated and the mix was put under hydrogen atmosphere using a balloon. The reaction was allowed to stir 48 hrs at which time the mix was filtered through silica/celite packed frit (hexanes/ethylacetate) affording the desired product as a red oil (3.87g, 97%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.97 (dd, J = 7.94 Hz, 1H), 6.36 (d, J = 7.9 Hz, 1H), 6.35 (d, J = 7.9 Hz, 1H), 3.80 (s, 3H), 3.62 (bs, 2H), 2.04 (s, 3H).

Example 106

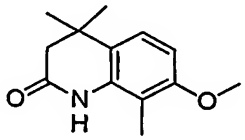
2-methyl-3-(3-methyl-2-butenamido)anisole (Compound 206)



3-methoxy-2-methylaniline (3.87g, 28 mmol) was taken up in acetone and cooled to 0C using a water/ice bath under nitrogen. Potassium carbonate (5.86g, 42 mmol) was added, followed by addition of 3,3-Dimethylacryloylchloride (3.78mls, 34mmol). The reaction was allowed to warm to room temperature and stir for 12 hrs. The mix was concentrated under reduced pressure to an off white solid. The solid was purified using a silica packed plug (hexanes/EtoAc) affording a dull orange solid, which was recrystallized from hexanes and a minimal amount of ethylacetate to generate 2-methyl-3-(3-methyl-2-butenamido) anisole as crystals (2.6g, yield: 42%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (bs, 1H), 7.14 (dd, J = 8.2 Hz, 1H), 6.84 (bs, 1H), 6.68 (bd, J = 7.94 Hz, 1H), 5.74 (bs, 1H), 3.81 (s, 3H), 2.20 (d, J = 0.9 Hz, 3H), 2.11 (s, 3H), 1.89 (bs, 3H), 1.56 (bs, 2H).

Example 107

4,4,8-trimethyl-7-methoxy-3,3-dihydroquinolone (Compound 207)

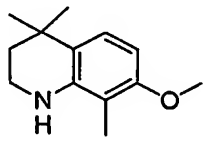


The amide (2.5g, 11.5mmol) was taken up in dry methylene chloride (60ml) in a flame dried flask under nitrogen and aluminum chloride (15.2g, 115mmol) was added. The reaction was heated to reflux for 1.5 hrs at which time the reaction was poured over ice. The water ethylacetate mix was extracted three times with ethyl acetate (100mls/X3) from water, the organic layers were collected and washed with brine, dried over solid sodium sulfate, filtered, and concentrated under reduced pressure to a solid. The solid was recrystallized from 50%Etoac/Hexanes to afford the desired product as a crystal

(1.65g, yield: 66%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (bs, 1H), 7.10 (d, J = 8.5 Hz, 1H), 6.58 (d, J = 8.5 Hz, 1H), 3.82 (s, 3H), 2.46 (s, 2H), 2.10 (s, 3H), 1.30 (s, 6H).

Example 108

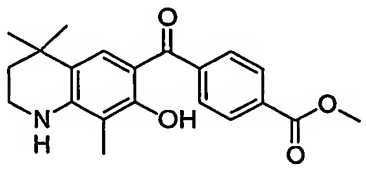
4,4,8-trimethyl-7-methoxy-1,2,3-tetrahydroquinoline (Compound 208)



4,4,8-trimethyl-7-methoxy-3,3-dihydroquinolone (1g, 4.6mmol) was taken up in 23 ml dry THF under nitrogen in a flame dried flask and boranedimethylsulphide complex (22.8 ml of a 2 M solution in toluene, 46 mmol) was added and the reaction was heated to reflux for 4 hours. The reaction mixture was cooled and quenched with methanol (5 eq.) and the mixture was concentrated under reduced pressure to a clear oil. The oil was purified using a silica packed plug (hexanes/10%EtoAc/hexanes) to afford the desired 4,4,8-trimethyl-7-methoxy-1,2,3-tetrahydroquinoline as a clear oil (940 mg, quantitative). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.04 (d, J = 8.5 Hz, 1H), 6.28 (d, J = 8.5 Hz, 1H), 3.78 (s, 3H), 3.38 (m, 2H), 1.97 (s, 3H), 1.73 (m, 2H), 1.29 (s, 6H).

Example 109

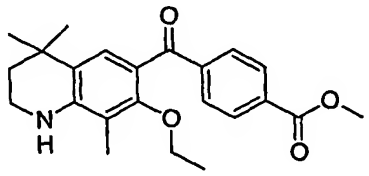
Methyl-6-(4,4,8-trimethyl-7-hydroxy-1,2,3,4-tetrahydroquinolino)benzoyl benzoate (Compound 209)



4,4,8-trimethyl-7-methoxy-1,2,3-tetrahydroquinoline (500mg, 2.4mmol) was taken up in 15 ml dry CH_2Cl_2 in a flame dried flask under nitrogen and the acid chloride (726mgs, 3.7mmol) was added followed by addition of aluminum chloride (3.25g, 24mmol). The reaction was heated to reflux for 8 hrs at which time the reaction was poured over ice. The mix was extracted three times with ethyl acetate (100mls/X3) from water, the organic layers were collected and washed with brine, dried over solid sodium sulfate, filtered, and concentrated under reduced pressure to a yellow solid. The solid was first purified using a flash silica column chromatography (EtoAc/Hex) and preparative HPLC (80%methanol/20%water) to afford the desired product as a yellow solid (50 mgs, 6%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.01 (s, 1H), 8.15 (d, J = 8.2 Hz, 2H), 7.66 (d, J = 8.2 Hz, 2H), 7.18 (s, 1H), 4.72 (s, 1H), 3.97 (s, 3H), 3.50 (m, 2H), 2.03 (s, 3H), 1.64 (m,2H), 1.16 (s, 6H).

Example 110

Methyl-6-(4,4,8-trimethyl-7-ethoxy-1,2,3,4-tetrahydroquinolino)benzoyl benzoate (Compound 210)

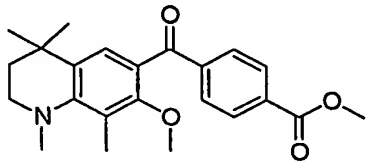


To a mixture of methyl-6-(4,4,8-trimethyl-7-hydroxy-1,2,3,4-tetrahydroquinolino)benzoyl benzoate (50mg, 0.14mmol) in DMF (2ml) under nitrogen was added Iodoethane (0.01mls, 0.16 mmol), and potassium carbonate (23mgs, 0.17mmol). The reaction was allowed to stir 48 hrs at which time the reaction was quenched with water and extracted three times with ethyl acetate (100mls/X3), the

organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to a yellow oil. The oil was purified twice using flash silica column chromatography (gradient Hexanes to 15% EtoAc/Hexanes) affording the desired product (32mg, 60%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (d, J = 8.2 Hz, 2H), 7.80 (d, J = 7.94 Hz, 2H), 7.41 (s, 1H), 4.3 (bs, 1H), 3.94 (s, 3H), 3.57 (q, J = 7.0 Hz, 2H), 3.48 (m, 2H), 2.00 (s, 3H), 1.74 (m, 2H), 1.29 (s, 6H), 0.90 (t, J = 7.0, 3H).

Example 111

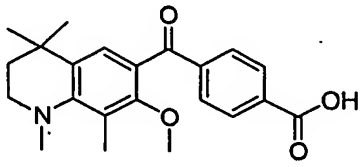
Methyl-6-(1,4,4,8-tetramethyl-7-methoxy-1,2,3,4-tetrahydroquinolino)benzoyl benzoate (Compound 211)



To a mixture of the Methyl-6-(4,4,8-trimethyl-7-hydroxy-1,2,3,4-tetrahydroquinolino)benzoyl benzoate (15 mg, 0.04 mmol) in DMF (2ml) under nitrogen was added methyliodide (0.01 ml, 0.17 mmol), and sodium hydride (8 mg, 0.17 mmol). The reaction was allowed to stir 2 hrs at which time the reaction was quenched with water and extracted three times with ethyl acetate (100ml/X3), the organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to a yellow oil. The oil was purified using flash silica column chromatography (gradient Hexanes to 10% EtoAc/Hexanes) affording methyl-6-(1,4,4,8-tetramethyl-7-methoxy-1,2,3,4-tetrahydroquinolino)benzoyl benzoate as a yellow oil (14mgs, 88%). ^{1}H NMR (500 MHz, $CDCl_3$) 8.1 (d, J = 8.2 Hz, 2H), 7.85 (d, J = 8.5 Hz, 2H), 7.30 (s, 1H), 3.95 (s, 3H), 3.51 (s, 3H), 3.20 (m, 2H), 2.86 (s, 3H), 2.20 (s, 3H), 1.70 (m, 2H), 1.26 (s, 6H).

Example 112

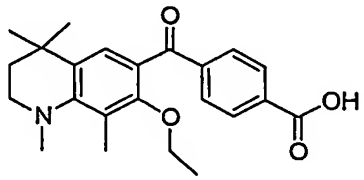
6-(1,4,4,8-tetramethyl-7-methoxy-1,2,3,4-tetrahydroquinolino)benzoyl benzoic acid (Compound 212)



To a solution of methyl-6-(1,4,4,8-tetramethyl-7-methoxy-1,2,3,4-tetrahydroquinolino)benzoyl benzoate (14 mg, 0.04 mmol) in a 1:1:1 mixture of THF/Water/Ethanol was added Lithium hydroxide (8 mg, 0.2 mmol). The reaction was allowed to stir at room temperature for 5 hrs at which time the reaction was quenched with water and acidified to pH 3 using 6N HCl. The solution was extracted three times with ethyl acetate (100mls/X3), the organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to the desired product; 6-(1,4,4,8-tetramethyl-7-methoxy-1,2,3,4-tetrahydroquinolino)benzoyl benzoic acid. ^1H NMR (500 MHz, $CDCl_3$) δ 8.17 (d, J = 8.2 Hz, 2H), 7.88 (d, J = 8.2 Hz, 2H), 7.33 (s, 1H), 3.51 (s, 3H), 3.22 (bs, 2H), 2.89 (s, 3H), 2.22 (s, 3H), 1.72 (s, 2H), 1.28 (s, 6H).

Example 113

6-(1,4,4,8-tetramethyl-7-ethoxy-1,2,3,4-tetrahydroquinolino)benzoyl benzoic acid (Compound 213)

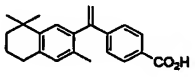


Example 113 was synthesized from methyl-6-(4,4,8-trimethyl-7-ethoxy-1,2,3,4-tetrahydroquinolino)benzoyl benzoate according to the procedure described for Example 112. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, J = 8.2 Hz, 2H), 7.81 (d, J = 7.93 Hz, 2H), 7.40 (s, 1H), 3.94 (s, 3H), 3.55 (q, J = 7.0 Hz, 2H), 3.48 (m, 2H), 2.00 (s, 3H), 1.74 (m, 2H), 1.29 (s, 6H), 0.90 (t, J = 7.0 Hz, 3H).

Example 114

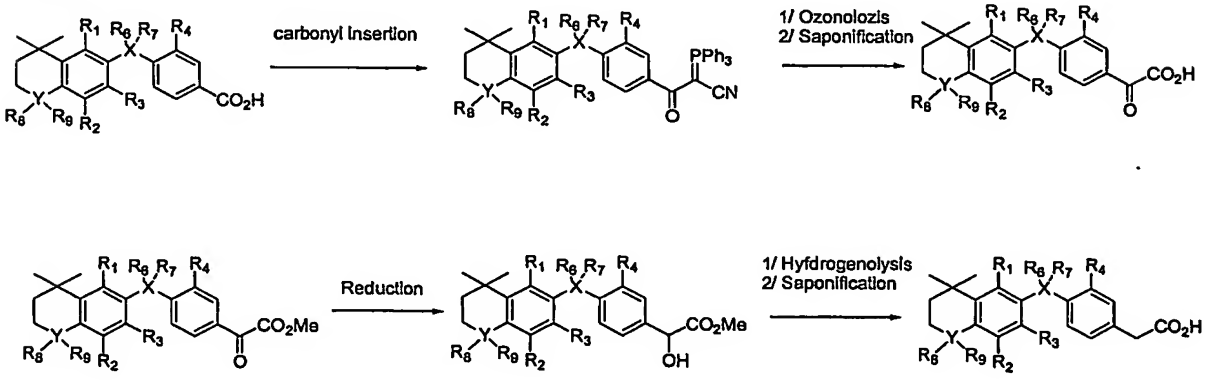
4-[(5,6,7,8-tetrahydro-3,8,8-trimethyl-2-naphthalenyl)ethenyl] benzoic acid (Compound 214)

Compound 214 was synthesized as described by Boehm and Al (*J. Med. Chem.*, 1995, **38**, 3146-3155), the entire disclosure of which is incorporated by reference herein.



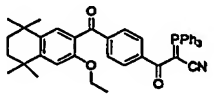
Compounds possessing R_5 as $C(R'_5R''_5)COOH$ may be synthesized using the following synthetic scheme:

Scheme 13



Example 115

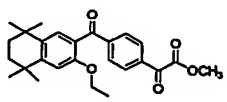
1-Cyano-1-(triphenylphosphoranylidene)-2-oxo-2-[4-[5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-3-ethyloxy-2-naphthalenyl]phenyl]ethane (compound 215)



To a solution of 4-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethyloxy-2-naphthalenyl]benzoyl benzoic acid (1.8998 g, 5.0 mmol, example 3) in 30 mL of CH_2Cl_2 was sequentially (cyanomethylene) triphenylphosphorane (1.6551 g, 5.5 mmol), DMAP (61.0 mg, 0.5 mmol) and triethylamine (0.76 mL, 5.5 mmol) followed by EDCI (1.0530 g, 5.5 mmol). The resulting mixture was stirred at 23° C for 24 h. After TLC analysis indicating the completion of reaction. The solvent was removed under reduced pressure. The residue was taken into 150 mL of ethyl acetate and washed with H_2O (3 x 80 mL) and brine (80 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was further purified by flash column chromatography (SiO2, 4 x 20 cm, 1:1 ratio of ethyl acetate : hexane as eluant) to give desired product 1.0332 g (31%, theo. 3.3144 g) as a white solid. ^1H NMR (500 MHz, $CDCl_3$) 8.02(d, *J*=8.8 Hz, 2H), 7.85(d, *J*=8.8 Hz, 2H), 7.75-7.55(m, 15H), 7.38(s, 1H), 6.85(s, 1H), 3.94(q, *J*=6.8 Hz, 2H), 1.71(m, 4H), 1.33(s, 6H), 1.27(s, 6H), 1.11(t, *J*=6.8 Hz, 3H).

Example 116

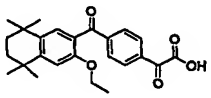
Methyl 2-oxo-2-[4-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethyloxy-2-naphthalenyl]phenyl]acetate (compound 216).



To a solution of 1-cyano-1-(triphenylphosphoranylidene)-2-oxo-2-[4-[5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-3-ethyloxy-2-naphthalenyl]phenyl]ethane (0.8208 g, 1.24 mmol) in 40 mL of a 1:1 ratio mixture of CH_2Cl_2:MeOH was cooled to –78° C in a dry ice/acetone bath. A stream of ozone was bubbled into reaction mixture for 10 min until a blue colored solution persisted. The reaction mixture was allowed to slowly warm to 23° C, meanwhile a stream of nitrogen was bubbled into the solution to remove excess ozone. The solvent was removed under reduced pressure. The residue was taken into 40 mL of THF and treated with 10 mL of 1.0 M aqueous $AgNO_3$ solution. This mixture was stirred at 23° C for 24h. Filtered through a pad of celite and the celite cake was further rinsed with 200 mL of EtOAc. The filtrate was washed with H2O (3x100 mL) and brine (100 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was further purified by flash column chromatography (SiO_2, 4 x 20 cm, 10% EtOAc/hexane as eluant) to give desired product 0.4072 g (78%, theo. 0.5225 g) as a pale yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) 8.08(d, *J*=8.3 Hz, 2H), 7.88(d, *J*=8.3 Hz, 2H), 7.48(s, 1H), 6.84(s, 1H), 4.02 (s, 3H), 3.90(q, *J*=6.8 Hz, 2H), 1.73(m, 4H), 1.33(s, 6H), 1.29(s, 6H), 0.98(t, *J*=6.8 Hz, 3H).

Example 117

2-Oxo-2-[4-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethyloxy-2-naphthalenyl]phenyl]acetic acid (compound 217)

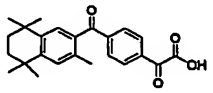


Saponification of methyl 2-oxo-2-[4-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethyloxy-2-naphthalenyl] phenyl]acetate according to the procedure described in Example 3 affords 2-Oxo-2-[4-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethyloxy-2-

naphthalenyl]phenyl]acetic acid as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) 7.82(d, J=8.8 Hz, 2H), 7.73(d, J=8.8 Hz, 2H), 7.36(s, 1H), 7.01(s, 1H), 3.93(q, J=6.8 Hz, 2H), 1.67(m, 4H), 1.31(s, 6H), 1.23(s, 6H), 0.83(t, J=6.8 Hz, 3H).

Example 118

2-Oxo-2-[4-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-methyl-2-naphthalenyl]phenyl]acetic acid (compound 218)



Compound 218 was synthesized from 4-[5,6,7,8-Tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl]benzoyl benzoic acid according to the procedure described for the synthesis of Compound 217. ^{1}H NMR (500 MHz, DMSO-d_6) 8.10(d, J=8.8 Hz, 2H), 7.87(d, J=8.8 Hz, 2H), 7.34(s, 1H), 7.28(s, 1H), 2.26(s, 3H), 1.66(m, 4H), 1.29(s, 6H), 1.17(s, 6H).

Example 119

Binding Assays

[0192] Compounds of the invention were separately incubated with HNF-4α at varying concentrations in the presence of varying concentrations of radiolabeled methyl 4-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethyloxy-2-naphthalenyl]benzoyl benzoate (Compound 103; Example 3) to determine each compound's binding affinity for HNF-4α. Compounds were also separately incubated with RXRα in the presence of varying concentrations of radiolabeled 9-cis-retinoic acid to determine each compound's binding affinity for RXRα. Data for 20 compounds is provided in Table 1.

Compound No.	HNF-4α binding[1] Ki (nM)	RXRα Binding[2] Ki (nM)
103	110	824
104	710	> 30000
105	96	1500
108	165	>5000
110	163	>10000
124	5206	>30000
149	580	5200
155	1193	3000
160	339	2700
163	1398	6500
173	514	>10000
178	215	3000
179	1010	>30000
189	322	1900
190	244	4600
192	966	>30000
201	721	3000
203	2205	>30000
212	4600	>30000
217	364	>10000

Table 1: Binding affinity. [1] Ki determined using [^{3}H]-compound 103. [2] Ki determined using [^{3}H]-9-cis-RA.

Example 120

Co-Transfection

[0193] CV-1 cells (African green monkey kidney fibroblasts) were cultured in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% charcoal resin-stripped fetal bovine serum (CH-FBS) then transferred to 96-well microtiter plates one day prior to transfection.

[0194] To determine HNF-4α receptor agonist and antagonist activity of the compounds of the present invention, the CV-1 cells were transiently transfected by FuGENE 6 transfection reagent in 175 cm^2 flask with the following plasmids: pCMX-HNF-4αDF (3μg/flask), apoA1-LUC reporter (1μg/flask), and filler DNA (pcDNA; 3μg/flask). The receptor plasmid, pCMX-HNF-4αDF, contains the rat HNF-4α1 under constitutive control of the CMV promoter, as more fully described in Fraser *et al.*, "DNA binding and transcription activation specificity of hepatocyte nuclear factor 4" *Nucl. Acids Res.*, **26**: 2702-2707 (1998).

[0195] The reporter plasmid, apoA1-LUC, contains the cDNA for firefly luciferase (LUC) under control of a multimerized HNF-4α response element (the A site from the apo A1 promoter) linked to the TK minimal promoter. *See e.g.*, Fraser *et al.* supra. Twenty hours four after transfection, the cells were harvested and plated in 96 well plates at 10,000 cells/well. Media containing reference compounds (compound 168) as an HNF-4α receptor antagonist; and/or the modulator compounds of the present invention in concentrations ranging from 10^{-10} to 10^{-5} M were added to the cells. Three to four replicates were used for each sample. Transfections and subsequent procedures were performed on a Biomek 1000 automated laboratory work station.

[0196] After 24 hours, the cells were washed with PBS, lysed with a Triton X-100-based buffer and assayed for LUC activity using a NORTHSTAR HTS workstation.

[0197] The mean and standard error of the mean (SEM) of the luciferase response were calculated. Data were plotted as the response of the compound compared to the reference compounds over the range of the dose-response curve. For agonist experiments, the effective concentration that produced 50% of the maximum response (EC_{50}) was quantified. Agonist efficacy was a function (%) of LUC expression relative to the maximum LUC production by the reference agonist. Antagonist activity was determined by testing the amount of LUC expression in the absence of exogenous compound (presence only of any endogenous ligand) as HNF-4α receptor agonist. The concentration of a test compound that inhibited 50% of LUC expression was quantified (IC_{50}). In addition, the efficacy of antagonists was determined as a function (%) of maximal inhibition. Data for 18 compounds are reported in Table 2.

Table 2: Agonist, partial agonist, antagonist and binding activity of HNF-4α receptor modulator compounds of present invention and the reference agonist compound, (compound 103) and reference antagonist compounds (compound 173). Efficacy (%) for HNF-4α agonist is determined by comparing activity (*e.g.*, luciferase production) of putative agonist to that LG0100695. Efficacy (%) for HNF-4α antagonist is determined by the percentage amount by which the luciferase production was reduced (maximum concentration of antagonist) from the luciferase production without compound.

Cmpd	HNF-4α Agonist CV-1 Cells		HNF-4α Antagonist CV-1 Cells	
No.	Efficacy (%)	Potency (nM)	Efficacy (%)	Potency (nM)
103	100	263		
104	103	2645		
105	33	2194		
108	43	2234		
110	57	594		
201	68	2237		
203	88	2948		
212	42	2848		
217	95	1142		
124			121	22
149			1061	4
160			108	4
173			100	103
178			110	1
179			103	19
189			120	1
190			119	3
192			118	35

[1] na = not active (*i.e.* efficacy of <20 and potency of >10,000 nM for the cotransfection assay and K_i > 1000 nM for the binding assay)
nd = not determined

[0198] The present invention includes any combination of the various species and subgeneric groupings falling within the generic disclosure. This invention therefore includes the generic description of the invention with a proviso or negative limitation removing any subject matter from the genus, regardless of whether or not the excised material is specifically recited herein.

[0199] While in accordance with the patent statutes, description of the various embodiments and processing conditions have been provided, the scope of the invention is not to be limited thereto or thereby. Modifications and alterations of the present invention will be apparent to those skilled in the art without departing from the scope and spirit of the present invention.

[0200] Therefore, it will be appreciated that the scope of this invention is to be defined by the appended claims, rather than by the specific examples which have been presented merely to illustrate certain embodiments of the present invention.